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Pterygium Recurrence- Surgical and Adjuvant Therapies

Dishani Pardhi [a*‡] and Shruti Sanghavi [b†]

[a] Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to Be University), Sawangi (Meghe), Wardha– 442001, Maharashtra, India.
[b] Department of Ophthalmology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to Be University), Sawangi (Meghe), Wardha– 442001, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Purpose: Pterygium is a prevalent disease of the eye that challenges ophthalmologists in its management due to its high tendency to reoccur. We performed an analysis to identify among the various surgical and adjuvant treatments the best combination that has the most pterygium recurrence prevention
Methods: A search was run through Pubmed, Google Scholar, ClinicalTrials.gov, and World Health Organisation for Randomised control trials and other literature comparing surgical and adjuvant treatments for pterygium. This data was then analyzed to ascertain the various advantages and disadvantages of different surgeries and adjuvant therapies over each other.
Results: Following the data analysis, we found out that the order of surgical methods from best to worst is as follows: Conjuctivalautograft>Amniotic membrane autograft>bare sclera. Among the adjuvant therapies studied, we found that the order of effectivity is Mitomycin C followed by anti-VEGF, radiation therapy, and finally 5 Fluorouracil.
Conclusion: Bare scleral excision alone has the highest recurrence rate, followed by Amniotic Autograft and conjunctival autograft. The adjuvants that can reduce pterygium recurrences are Mitomycin C, Anti VEGF, 5-Fluorouracil, and radiation therapy with Mitomycin C, the most

‡ MBBS Student;
† Senior Resident (Cornea and Refractive Surgeon);
**Corresponding author: E-mail: dishani149@gmail.com;*

frequently used and with lesser late complications. More studies with larger samples and long-term follow-ups directly compare these surgical and adjuvant treatments to develop more uniform guidelines for forming treatment plans.

Keywords: Pterygium; pterygium recurrence; bare sclera excision; amniotic membrane graft; conjunctival autograft; mitomycin C; 5-fluorouracil; anti-VEGF; radiations.

1. INTRODUCTION

1.1 Background

Pterygium is a degenerative condition of the conjunctiva in which a triangular-shaped wing encroaches the cornea within the intrapalpebral fissure from either side.

Pathologically it is a degenerative condition characterized by hyperplasia of the conjunctiva. The subconjunctival tissue undergoes elastic degeneration and proliferates as vascularized granulation tissue under the epithelium, eventually invading the cornea.

One of the critical features of pterygium is localized limbal failure and centripetal encroachment of the cornea by altered limbal epithelial cells, which exhibit squamous metaplasia and goblet cell hyperplasia, which co-occurs along with the disintegration of Bowman's layer and growing abundance of stromal activated fibroblasts, atypical extracellular matrix accumulation, inflammatory cell infiltrates, neovascularization and elastosis [1].

With reoccurrence rates as high as 88% in some populations after surgical removal [2], various surgical options and adjuvant therapies are used to treat the pterygium and prevent its reoccurrence. The existence of pterygium is distressing to the patient because of its unattractive appearance and the ophthalmologist because of its likeliness to reoccur [3].

It is essential to ascertain the best possible therapy in which reoccurrence is the least as it has been shown that cases of recurrent pterygium are more challenging to treat as compared to primary cases of pterygium [4].

2. METHODS

Literature searches were done in July and August 2021. We searched Pubmed, Google Scholar, ClinicalTrials.gov, and World Health Organisation. The MeSH terms pterygium, as well as recurrence, were used. We went through abstracts of citations and cases requiring complete texts to deduce RCTs and reviews in which recurrences were reported as an outcome measure. The primary interventions studied were bare sclera excision, conjunctival autograft, limbal autograft, amniotic membrane graft, and adjunctive use of Mitomycin C, 5-Fluorouracil, anti-VEGF as well as radiation.

2.1 Questions for Assessment

What are surgical and adjuvant treatments best for preventing recurrence of pterygium?

2.2 Bare Sclera Excision

It is one of the initial techniques employed in removing the growth and is recognized by simple excision, following which the scleral bed is allowed to epithelialize again [5]. Some researchers have reported that the bare sclera technique is linked with higher recurrence rates, reduced when adjuvants are used [6]. The risk of developing pterygium recurrence is higher when only bare sclera excision is performed without the administration of any adjuvants. The reoccurrence rate of pterygium following bare sclera excision becomes significantly higher with the fleshiness of the sclera [7]. Since pterygium recurrence rate is significantly high in patients who undergo only bare sclera excision, it is no longer used as the only or sole treatment of pterygium. It is usually combined with adjuvant therapies to give better results.

2.3 Conjunctival Autograft

Schemer et al. demonstrated the limbal location of corneal epithelial cells [8]. It has been understood that prolonged exposure to UV radiations leads to locally acquired stem cells' insufficiency, which acts as a barrier between the corneal epithelium and the conjunctiva. Limbal tissue degeneration promotes conjunctival tissue growth onto the cornea [9,10]. Kenyon et al. made this the foundation for incorporating limbal stem cells present in the limbal tissue into the graft of the free conjunctiva [11].

The recurrence rates reported by Pandey et al., Tan et al., Chen et al., and Mutlu et al. were 5%, 2%, 2.1%, and14.6%, respectively [12,7,13,14].

The post excision recurrence rate reported by Kam et al. was 6.5% when Conjuctivalautograft was used alone but 0% when it was accompanied with Mitomycin C use. Kheirkhah et al. also gave an account of 25% recurrence when conjunctival autograft was used alone but reduced recurrence in the group with accompanied mitomycin C use [15-16].

This suggests that Conjunctival autograft, when accompanied with mitomycin C use, is significantly effective in reducing recurrence.

In Australia, an extensive study took place with a surgical excision technique called P.E.R.F.E.C.T. (Pterygium Extended Removal Followed by Extended Conjunctival Transplantation) in which the cases were followed up for more than one year, and reoccurrences reported were as low as 0.4% [17].

Compared with bare sclera excision, this technique has more long time efficacy and less recurrence rate. The surgical duration of this method is longer than bare scleral excision and requires technical expertise [14,16,18].

2.4 Amniotic Membrane Transplant

The innermost layer of the placenta, the Amniotic membrane, has anti-inflammatory and anti-fibrotic properties and can be used as a graft. It can promote epithelial cell multiplication and differentiation by providing a lot of growth factors without having the risk of immunological reaction [5]. The expression of TGF-βsignalling and alteration of the myofibroblast in pterygium is effectively subdued by the matrix of the amniotic membrane stroma [19]. During transplantation, the graft must be placed over the bare sclera so that the basement membrane faces up and the storm faces down. Fibrin glue or sutures may be used for fixation.

Recurrence rates following AMT vary from 3.8% to 40.9% in different studies. Prabhasawat et al. observed recurrence of 10.9% following amniotic membrane collocation [20]. This technique was subsequently modified by Solomon et al. to achieve a reduced recurrence rate of 3% [21]. Having said that, when compared with conjunctival autografts, the advantage of AMTremainsdisputed [22].

Three randomized clinical trials compared recurrences after AMT and conjunctival autograft procedures. All of the studies observed lesser recurrence in conjunctival autograft [18]. In certain circumstances, an Amniotic membrane graft shows more assurance over other grafting procedures, such as when already existing fibrosis of the conjunctiva makes it difficult to harvest the conjunctiva from the donor site for grafting. Grafting with the amniotic membrane is applicable even in trabeculectomy for filtering glaucoma where the superior conjunctiva must be spared and in cases of double-headed or when the pterygium is quite large [21]. The use of AM in association with Mitomycin C has reduced recurrence [23]. No significant complications have been reported in the literature when amniotic membrane transplant is done following pterygium excision, and this procedure has been observed to be a well tolerated technique.

3. ADJUVANTS

3.1 Mitomycin C

Almond MC et al. in the 1960s suggested Mitomycin C, an antibacterial and antineoplastic drug derived from *Streptomyces caespitosus,* as adjuvant therapy for pterygium [24]. Mitomycin is the most commonly used adjuvant in pterygium treatment. Several randomized control trials compared recurrence rates using different protocols assessing the effectiveness of intraoperative or postoperative Mitomycin C. In the study conducted by Frucht-Pery J et al. in 1994, patients that received a sole dosage of topical 0.02%MitomycinC for 5 minutes at the end of the surgery, the recurrence rate was down to 5%. This study points at the possible benefit of a single dose of 0.02% mitomycin C administration for postoperative prevention of pterygium recurrence [25]. M Helal et al. carried out a study to compare the efficacy of Mitomycin C administration intra opérative topical Mitomycin C postoperatively to treat pterygium**.** They concluded that an adequate alternative adjunctive treatment for pterygium is a single and intraoperative administration of MMC [26]. A study conducted in 1994 also indicated that administration of a single dose of 0.02% MMC intraoperatively effectively prevents pterygium recurrence [2]. However, according to another study, 0.01% of mitomycin C intraoperatively has comparatively better results than 0.02% Mitomycin C (recurrence being 4% and 8%, respectively) [27]. Another study that further

reduced the concentration of mitomycin to 0.05% also saw reduced recurrence; however, the only complication being corneal Dellen [28] P P Chen reported that the complications of mitomycin C: temporary and prolonged discomfort, build-up of pigment, watering of eyes, hyperemia, subconjunctival hemorrhage, and wound dehiscence. The higher the dosage higher is the persistence and intensity of the discomfort. Therefore, it was advised that only pterygia with higher risk should be administered with Mitomycin C. Single-dose up to 0.05 ml at a concentration of 0.5 mg/ml subconjunctival has the same results as multiple dosages with much less morbidity [5]. The most common complications after MMC administration is photophobia, irritation postoperative, and uneasiness in eyes with exacerbated watering, mainly if used at lower doses. Serious complications include cataract, corneal opacification, symblepharon, thinning of the sclera or its necrosis, anterior uveitis, ulceration of the cornea, sustained pain, and continued defects of conjunctiva and sclera. Many studies suggest that prolonged exposure of MMCin terms of dosage or period is linked to lesser reoccurrences. However, the chances of complications are more significant [4]. It has been shown in data from studies that there is an increased reduction in reoccurrence post excision when conjunctival autografts are used in combination with Mitomycin Crater than administration of MMC singly suggesting that reoccurrence is lesser when an adequate surgical technique is used along with MMC [29].

3.2 5Fluorouracil

The fluoropyrimidine, five fluorouracil (5-FU), is an anti-metabolite drug that leads to fibroblasts' apoptosis by hindering DNA and RNA production of fibroblasts [30]. Quite a few studies have taken place to understand 5-FU effectiveness in pterygium management. Prabhasawat et al. conducted a study that indicated that follow-up patients on treatment with 5-FU showed notably less recurrence with 5-FU administered once a week for two weeks compared to the group observed as control [31]. On Kaplan-Meier survival analysis, it was observed that the duration of reoccurrence free period of pterygium in the five fluorouracil group was more as compared to the group observed as control. Said et al. conducted a study in which it was presented that 93.3% of cases hada reduction of fibrovascular tissue and halting of growth after 0.1-0.2 ml or 2.5-5 mg 5 FU [32]. Low dose intra-operative 5-FU effectiveness was studied by Maldonado et al. and concluded that it was inefficient in preventing reoccurrence however it may be due to low dosage as well as time span of treatment suggesting that only one injection may not be sufficient [33]. It wasalsofound by a studythat 5-Fluorouracil injection intra lesional also improved cosmetic appearance of not only primary but of recurrentpterygia as well [25]. Epithelial keratopathy is one of the unfavorable effects seen with the used of 5fluorouracil is due to suppression of mitosis of corneal epithelium however this is more likely to be observed after its application in trabeculectomy done to treat glaucoma [34].

3.3 Anti- VEGF

In pterygium, both lymphatic vessels and blood vessels formation happen however angiogenesis is the event of importance, corresponding to the increased expression of vascular endothelial CD31 and increased blood to lymphatic vessel ratio. It was suggested Javier Martin Lopez et al that existence of elevated levels of VEGF-A in vessel networks as well as the extracellular matrix in the pterygium tissue might have a major impact on angiogenesis [35].

According to the study carried out by S A Malozhen et al there is 3% of chance of relapse of pterygium among patients who underwent LKP combined with anti-VEGF therapy. The utilisation of anti-Vascular endothelial growth factor agents as adjuvant therapy in surgically treating pterygium is a relatively safer technique of reducing postoperative inflammation, fibrovascular proliferation and eventually the amount of relapses [36].

3.4 Radiations

Radiotherapy is given in very less doses with the objectives of managing the condition and at the same time reducing late tissue conditions in benign conditions of the eye, such as petrygium [29].

In a study in which 975 cases of pterygia were surgically treated and immediately followed by strontium 90, data collected suggested that the recurrence was 6 % and the reoccurrences actually requiring surgery was 0.84% [24]. F D MacKenzie et al conducted a study in 1991 and reported that in patients treated with beta irradiation with a mean dose of 22 Gray, reoccurrence rate was 12%. Including 4.5% of

Table 1. Treatment plan

Procedure	Advantages	Disadvantages
Bare scleral excision	Less complicated and lesser surgical duration	Highest rate of reoccurance More complications
Conjunctival Autograft	Easy to perform Recurrence rates are less Better cosmesis Less graft displacement	Longer surgical time Difficult to cover defects that are larger
Amniotic Membrane autograft	Least complicated among the three techniques Lesser surgical duration Can be used in patients with short conjunctiva Any sized ocular surface defect can be covered by AMG More effective in certain cases Chances of graft displacement are high	Recurrence rates are high Complications Risk of graft loss or displacement

Table 2. Adjuvant therapy

Adjuvant Therapy	Advantages	Disadvantages
MMC	Reduction of reoccurrence is significant Most widely used and studied	Cannot be used in eyes with thin sclera or patients with other prexisting eye conditions Low tolerance
5 Fluorouracil	Lesser Toxicity	Disputed efficacy Cannot be used in eyes with thin sclera or patients with prexisting eye conditions Evidence is limited
Anti VEGF	Significant recurrence rate reduction Reduces post operative inflammation Good tolerance	Expensive Injection timing is not uniform
Radiation	Significant recurrence rate reduction	Late onset complications are more Coreneoscleral necrosis

the study group who had severe thinning, additional 13% showed signs of scleromalacia [37]. Surgical excision combined with appropriate administration of Strontium-90 is quite efficient in managingpterygium.2000 centigrayto 6000 centigray seems to be the most optimal dosage [38]. Late complications of ration therapy are scleralulceration,iris atrophy, cataract induced by radiations along with vision reduction, ptosis, opacities in sectorial lens but with normal visual acuity andsymblepharon.Patients with scleral ulceration may report Pseudomonas endopthalmitis. Iatrogenic ocular diseasemay be caused commonly by beta irradiation that are used to preventreoccurrence of pterygium [39]. However D J Levine in contrasted has suggested that substantially larger blanket of radiation produced by applicators is a major contributing factor to increased incidence of scleral necrosis. He suggested that placing the applicator at the limbus appears to be adequate in preventing most recurrences and also reduce scleral necrosis [40]. There needs to be more consensus on the dose as well as the effective time of exposure to radiation for effective treatment [41,42].

4. CONCLUSION

Of all the techniques studied during this analysis, Bare scleral technique seems to be associated with worst outcome and report higher recurrences especially when it is not associated with any other follow up adjuvant therapy. Among the three surgical techniques studied Conjunctival autograft shows the least recurrence rates and prevents graft displacement. Amniotic membrane graft shows

more assurance over other grafting procedures such as when already existing fibrosis of the conjunctiva makes it difficult to harvestthe conjunctiva from donor site for grafting. Grafting with amniotic membrane is useful even intrabeculectomy for filtering glaucoma were the superior conjunctiva must be spared, and in cases of double-headed or when the pterygium is quite large. Among the adjuvant therapies used Mitomycin C seems to be the most widely used however subconjunctival anti VEGF injections are relatively more safe and efficient adjuvant treatment. Use of 5-Fluorouracil also reported reduction in recurrence rate and the adverse effects reported have mostly been minor or temporary however is it is recommended that 5-Fluorouracil should not be used in combination surgeries where the patient may have history of other corneal diseases as the dosage used increases leading to complications. Radiation therapy report more late onset complications and there needs to more studies to determine the most optimum dosage.

There need to more studies with larger study sample and long term follow ups that directly compare these surgical and adjuvant treatments to come up with more uniform guidelines to form treatment plans.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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