Review Article

Pterygium recurrence- surgical and adjuvant therapies

Abstract

Purpose- Pterygium is a very common disease of the eye that poses a challenge to ophthalmologists in its management due to its high tendences to reoccur. We performed an analysis to identify among the various surgical and adjuvant treatments the best combination that has the most pterygiumrecurrence 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 analysed to ascertain the various advantages and disadvantages of different surgeries and adjuvant therapies over each other.

Result- Following analysis of the data 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 the order of effectivity is Mitomycin C followed by anti-VEGF followed by radiation therapy and finally 5 Fluorouracil.

Conclusion- Bare scleral excision alone has the highest recurrence rate followed by Amniotic Autograft followed by conjunctival autograft. The adjuvants that can used to reduce pterygium recurrences are Mitomycin C, Anti VEGF, 5-Fluorouracil and radiation therapy with Mitomycin C is the most frequently used and with lesser late complications. 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.

Keywords- Pterygium, Pterygium recurrence, Bare Sclera Excision, Amniotic Membrane Graft, Conjunctival Autograft, Mitomycin C, 5-Flourouracil, Anti-VEGF, Radiations

Background

Petrygium 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 characterised by hyperplasia of the conjunctiva. The subconjunctival tissue undergoes elastic degeneration and proliferates as vascularised granulation tissue under the epithelium which eventually invades the cornea.

One of the key 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 withthe disintegration of Bowman's layer and growth abundance of stromal activated fibroblasts, atypical extracellular matrix accumulation, inflammatory cell infiltrates, neovascularisation 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 in combination with the aim of treating the pterygium and also preventing its reoccurrence . The existence of pterygium is distressing to the patient because of its unattractive appearance as well as the ophthalmologist because of its likeliness to reoccur. [3]

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

Methods and methodology

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 in cases that required, complete texts to deduce RCTs as well as reviews in which recurrences were reported as an outcome measure. The main interventions studied were bare sclera excision, conjunctival autograft, limbalautograft, amniotic membrane graft and adjunctive use of Mitomycin C, 5-Fluorouracil, anti VEGF as well as radiation

Questions for assessment

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

Bare sclera excision

It is one of the initial techniques employed in the removal of the growth and is recognised by plain excision following which the scleral bed is allowed to epithelialize again. [5] It has been reported by quite some researches that thebaresclera technique is linked with higher recurrence rates, which is 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. Reoccurrence rate of pterygium following bare sclera excision becomes significantly higher with the fleshiness of the sclera.[7]. Since the rate of recurrence of pterygium is significantly high in patients that undergo only bare sclera excision, it now no longer used as the only or sole treatment of pterygium. It is usually combined with adjuvant therapies to give better results.

Conjunctival autograft

Schemer et al demonstrated the limbal location of corneal epithelial cells.[8] It has been understood that long time exposure to UV radiations leads to acquired stem cells insufficiency locally which under normal conditions acts as barrier between the corneal epithelium and the conjunctiva. Limbal tissue degeneration promotes the 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 is 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 an excision surgical technique called P.E.R.F.E.C.T. (**Pterygium Extended RemovalFollowed by Extended Conjunctival Transplantation)**in which the cases were followed up for a period of more than one year and reoccurrences reported were as low as 0.4%. [17]

When compared with bare scleral 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]

Amniotic membrane transplant

The innermost layer of the placenta, the Amniotic membrane, has anti inflammatory and anti fibrotic properties and can be used as graft. It has the ability to 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 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 in such a manner that the basement membrane faces up and the storma faces down. Fibrin glue or sutures may be used for fixation.
Reports of 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 randomised clinical trials compared recurrences after AMT and conjunctival autograft procedures. All of the studies observed lesser recurrence in conjunctival autograft[18]. In certain circumstances, 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 donor site for grafting. Grafting with amniotic membrane is useful even in trabeculectomy for filtering glaucoma were the superior conjunctiva must be spared, and in cases of double-headed or when the pterygium is quite large..[21]Use of AM in association with Mitomycin C has shown to to reduce recurrence [23]No major complications have been reported in literature when amniotic membrane tranplant is done following pterygium excision and this procedure been observed to be a well tolerated technique.

Adjuvants

1. **Mitocycin C-**
   Almond MC et al in 1960s suggested Mitomycin C, an antibacterial and anti neoplastic drug derived from *Streptomyces caespitosus*, as adjuvant therapy for pterygium[24].Mitomycin is the most commonly used adjuvant in pterygium treatment. There are several randomized control trials that 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 recurrence of pterygium. [25] M Helal et al carried out a study to compare the efficacy of Mitomycin C administration intra operativelyvs topical Mitomycin C postoperatively to treat pterygium**.** They came to the conclusion that effective 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% MMCintraoperatively effectively prevent spterygiumrecurrence.[2] However according to another study 0.01% of mitomycin C intra operatively 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 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 subconjunctivally has the same results as multiple dosage, however with much less morbidity.[5] The most common complications after
MMC administration are: photophobia, irritation postoperative and uneasiness in eyes with exacerbated watering specially 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 time span,is linkedto lesser reoccurrences, however the chances of complications are greater. [4] It has been shown in data from studies that there is increased reduction in reoccurrence post excision when conjunctival autograftis used in combination with Mitomycin Crather than administration of MMC singly suggesting that reoccurrence is lesser when as adequate surgical technique is used along with MMC[29]

2. 5Fluorouracil

The fluoropyrimidine, 5 fluorouracil (5-FU) is an anti-metabolite drug that leads to fibroblasts apoptosis by hindering DNA as well as RNA production of fibroblasts. [30] Quite a few studies have taken place to understand 5-FU effectiveness inpterygium management. Prabhasawat et al. conducted a study that showed results that indicated thaton follow up, patients on treatment with 5-FU showed notably less recurrence with 5-FU administered once a week for two weeks as compared to the group observed as control [31]. On Kaplan-Meier survival analysis it was observed that the duration of reoccurance free period of pterygium in the 5 fluorouracil group was more ascompared to the the group observed as control. Said et al conducted a study in which it was presented that 93.3% of caseshad reduction of fibrovascular tissue and halting of growthafter 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 came to the conclusion that it was inefficient in preventing reoccurrence however it may be due todeficient dosage as well as time spanof treatment suggesting that only one injection may not be sufficient .[33] It wasalsofound by a studythat 5-Fluorouracil injection intra lesionally also improved cosmetic appearance of not only primary but of recurrentpterygia as well.[25] Epithelial keratopathy is one of the unfavourable effects seen with the used of 5flourouracil 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. 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]

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 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].

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.

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

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