International Journal Dental and Medical Sciences Research
Volume 4, Issue 1, Jan-Feb 2022 pp 505-510 www.ijdmsrjournal.com ISSN: 2582-6018

Recent Advances in Management of Pterygium

Dr. Payal Mukherji[1], Dr. Vivek Kumar[2], Dr. Suchitra Kumari[3]
1. Senior Resident, Department of Ophthalmology, SNMMCH, Dhanbad
2. Senior Resident, Department of Ophthalmology, RIO, RIMS, Ranchi
3. Junior Resident, Department of Ophthalmology, RIO, RIMS, Ranchi

Submitted: 01-02-2022 Revised: 07-02-2022 Accepted: 10-02-2022

ABSTRACT-
Pterygium is a wing-shaped, vascular, fleshy growth that originates on the conjunctiva and can spread to the corneal limbus and beyond, maybe into the pupillary area. Indications for pterygium excision include persistent discomfort, vision distortion and induction of irregular astigmatism and progressive growth towards the corneal center/visual axis, atypical appearance suggesting dysplasia, increasing size, restricted ocular motility and cosmesis.
Newer surgical techniques of pterygium excision includes- amniotic membrane grafting, ologen transplantation, tissue glue, PERFECT, autologous blood graft fixation, air assisted dissection, cauterization etc. Newer non surgical techniques of pterygium management includes topical dipyridamole.
Newer adjunctive therapies aimed to reduce pterygium recurrence includes topical loteprednol, bevacizumab, antibiotics such as doxycycline and insertion of multimicroporous expanded e-PTFE. Newer gene targeted therapies are under clinical trials such as CRISPR-cas9, APR-246/PRIMA-1^{Met}.

INTRODUCTION-

A pterygium is a wing-shaped, vascular, fleshy growth that originates on the conjunctiva and can spread to the corneal limbus and beyond, maybe into the pupillary area.[1] The pathogenesis of a pterygium is strongly correlated with UV-light exposure, although environmental traumas such as exposure to dust, wind, or other irritants that cause chronic inflammation may also be factors. The prevalence of pterygia increases steadily with proximity to the equator (due to the damaging effects of UV-B radiation, which causes mutations in the p53 tumor suppressor gene, thus facilitating the abnormal proliferation of limbal epithelium) and is more common in men than women, in persons 20-30 years of age (the most common age of onset), and in people who work outdoors. Histopathology of pterygium shows senile elastosis of the subepithelial fibrovascular connective tissue and Bowman's membrane is destroyed within the corneal component and vascularization is seen.[2]
A pterygium consists of three distinct parts: the cap, the head and the body/tail.[1]

- **The cap** or leading edge is a flat zone on the cornea that consists mainly of fibroblasts that invade and destroy Bowman's membrane.
- **The head** is a vascular area that lies behind the cap and is firmly attached to the cornea.
- **The body/tail** is the mobile area of the bulbar conjunctiva, which can be easily dissected from the underlying tissue.

Linear epithelial iron deposition (Stocker line) may be seen in the corneal epithelium anterior to the head of the pterygium. Fuchs islets are small discrete whitish flecks consisting of clusters of pterygial epithelial cells often present at the advancing edge.[3]

A unique feature of pterygium epithelial cell is its positive immunohistochemical staining for different types of matrix metalloproteinases that are absent in normal conjunctival, limbal or corneal cells.
Pterygia are usually asymptomatic in earlier stages, however there can be signs of dry eye (burning, itching, tearing). As the disease progresses, the lesion increases in size and becomes cosmetically unpleasant for the patient.[1,3] Further growth may cause visual symptoms due to induced astigmatism or direct encroachment onto the visual axis. Aggressive or recurrent pterygia may cause restrictive strabismus and distortion of the eyelids.
Indications for pterygium excision include persistent discomfort, vision distortion and induction of irregular astigmatism, significant (>3-4 mm) and progressive growth towards the corneal center/visual axis, atypical appearance suggesting dysplasia, increasing size (documented by an ophthalmologist), restricted ocular motility and cosmesis. The aim of microsurgical excision of a pterygium is to achieve a normal, topographically smooth ocular surface.[1]

International Journal Dental and Medical Sciences Research
Volume 4, Issue 1, Jan-Feb 2022 pp 505-510 www.ijdmsrjournal.com ISSN: 2582-6018

CONSERVATIVE MANAGEMENT:

Early in the disease process, ophthalmologists often take a conservative approach, limiting therapy to **lubricating medications**.[1] Since UV radiation is believed to be an important risk factor, the clinician should recommend that patients with early-stage pterygium use proper **protective eyewear** (ultraviolet blocking eyewear), **protective hats** etc.

SURGICAL EXCISION OF PTERYGIUM:

Excision of the pterygium is the first step for repair. Many ophthalmologists prefer to avulse the head from the underlying cornea. Advantages include quicker epithelialization, minimal scarring and a resultant smooth corneal surface.

Bare sclera technique: involves excising the head and body of the pterygium while allowing the bare scleral bed to re-epithelialize. No sutures or fine, absorbable sutures are used to appose the conjunctiva to the superficial sclera in front of the rectus tendon insertion, leaving an area of exposed sclera. High recurrence rates between 24 percent and 89 percent, have been documented in various reports and is therefore strongly not recommended.[1,2]

Conjunctival flap: The procedure involves obtaining an autograft, usually from the superotemporal bulbar conjunctiva with the same dimensions as the scleral bed, and suturing the graft over the exposed scleral bed after excision of the pterygium. Complications are infrequent. There has to be careful dissection of Tenon's tissue from the conjunctival graft and recipient bed, minimal manipulation of tissue and accurate orientation of the graft.[4] It has recurrence rates reported to be as low as 2 percent and as high as 40 percent in several prospective studies.

Conjunctivo-limbal autograft technique: 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 range from 0-15%.[5] In some situations, where there has been previous surgery, or limbal damage due to other causes, surgical manipulations when removing a limbal graft may promote further damage to stem cells. In this situation, Tan et al have suggested that the use of free conjunctival grafts may have equivalent outcomes. This technique may also be advantageous when surgery is performed in a patient with a subsequent risk of glaucoma and the need to preserve the superior bulbar conjunctiva.

Amniotic membrane grafting: As a natural basement membrane, amniotic membrane (AM) contains various matrix proteins which facilitate the adhesion, migration, differentiation, and prevention of apoptosis of epithelial cells.[1] The AM is also capable of binding growth factors which may help to promote wound healing. Unfortunately, recurrence rates vary widely among the studies that exist, somewhere between 2.6 percent and 10.7 percent for primary pterygia and as high as 37.5 percent for recurrent pterygia. A distinct advantage of this technique over the conjunctival autograft, however, is the preservation of bulbar conjunctiva. Amniotic membrane is typically placed over the bare sclera, with the basement membrane facing up and the stroma facing down. Some recent studies have advocated the use of fibrin glue to help the amniotic membrane graft adhere to the underlying episcleral tissue.

Ologen transplantation: Ologen is a three-dimensional porous collagen-glycosaminoglycan copolymer, taken from the matrix of porcine collagen, helps the reorganization of subconjunctival scar formation by separating the subconjunctival and episcleral tissues and inducing fibroblasts and myofibroblasts to grow in the structure after surgical excision of pterygium.[6] It provides a good growth environment for the fibroblasts in the eye and guides the fibroblasts to grow on the pores of the matrix in a discrete manner, so that the wound's healing process will be physiological, and the tissue scar will be inhibited. It is considered as a safe, simple and effective alternative to the use of fibrin glue. Ologen implantation is technically easier, provides short operative time compared with conjunctival autograft transplantation, and preserves healthy conjunctiva. Ologen implantation has the advantage of less complication and less recurrence, it may be a new, safe, and effective alternative for improving the short-term success rate of primary surgery.

Tissue (fibrin glue): Fibrin glue can replace or augment sutures when attaching conjunctival grafts or amniotic membrane, significantly shortening operating times and decreasing postoperative discomfort, as well as decreasing recurrence rates.[7] In general, fibrin glue consists of two main components: a sealer protein concentrate containing fibrinogen and a fibrinolysis inhibitor, and a thrombin and calcium chloride solution. When mixed at the time of application, the two solutions interact and mimic the clotting cascade,

creating adhesion, while allowing the surgeon from 10–60 seconds to complete membrane alignment and orientation. The clot then dissolves after 1–2 weeks, providing adequate time for healing[8]. Since fibrin adhesives are prepared from pooled donor sources, there is a small but finite risk of infection, such as hepatitis and HIV, as well as of anaphylactic reaction. The infection risk is reduced by testing donors for viral markers, at the time of donation and 6 months later, as well as by sterilization of the products by gamma irradiation and treatment with detergents or solvents.

Autoblood graft fixation: The newest approach is autoblood graft fixation, a technique also known as suture-free and glue-free autologous graft.[9] With this approach, after the pterygium and associated conjunctiva are excised, the surgeon allows a thin film of blood clot to form over the bare area. Any active bleeding is stopped by direct tamponade.[9] Next, a thin, Tenon-free conjunctival autograft, with or without inclusion of limbal stem cells, is fashioned. After the graft is aligned, it is placed over the blood film in the bare area, and the edges are held with forceps, usually for three to five minutes, to give adequate time for graft fixation to occur. Patients who regularly take aspirin or other blood thinners or who suffer from a coagulation factor deficiency would not be good candidates for autoblood graft fixation. The main disadvantage is the risk of graft loss in the immediate postoperative period. If properly performed, the procedure appears to carry a low risk of recurrence.

Cauterization: Another sutureless method that can be used in pterygium surgery involves cauterization.[10] Bipolar cautery causes thermal welding, which results in vapourising intracellular fluid and denaturation of tissue proteins. Cautery autograft fixation has reduced postoperative discomfort compared with autograft fixation with sutures, fibrin glue and autologous fibrin glue. Idea of hybrid technique for joined suturing and cauterisation has been presented for large pterygia, and further usage of bipolar cautery has been proposed. Cauterisation used for fixation of amniotic membrane transplant after pterygium excision showed no recurrence, dislocation or malposition of a transplant.[10] Therefore, cauterisation autografting can be at least as effective as fibrin glue autografting in terms of recurrence, complication rate, postoperative discomfort with no risk of transmitting infectious agents and causing anaphylaxis in susceptible individuals.

P.E.R.F.E.C.T. Surgery: P.E.R.F.E.C.T. stands for 'Pterygium Extended Removal Followed by Extended Conjunctival Transplant'.[11] Lawrence W. Hirst et al, reported data from a prospective study in which 250 patients underwent pterygium surgery with what Dr. Hirst called the PERFECT technique (pterygium extended removal followed by extended conjunctival transplant). In this approach, an extensive conjunctival autografting of about 15mm by 12mm is done.[4] The advantages of this approach are less recurrence rate (0.5%) and a better cosmetic outcome as graft edge and the surgical scars are hidden in the fornices and caruncle. The main limitation is that this is time consuming and technically challenging procedure.

Minimally invasive pterygium surgery: This is carried out by making a limbal incision of the conjunctiva through the body of pterygium and removing the head of the pterygium by blunt dissection, keeping the adjacent tenon capsule intact.[11] A small conjunctival autograft was performed to cover the epithelial defect. Minimally invasive pterygium surgery had lower recurrence rate and fewer postoperative complications, preserving the tenon capsule and minimizing conjunctival excision in pterygium surgery. Autograft is easier to perform in minimally invasive surgery of pterygia.[11]

Air-assisted dissection technique: Air-assisted dissection technique removes the pterygium head and facilitates the establishment of a smooth and clear corneal surface without extrascraping or polishing. Air is injected into the side of the cap of the pterygium head with a 30 G needle, to create a dissection plane between the pterygium head and the cornea. After blunt dissection and excision of the pterygium, the conjunctival autograft technique is applied.[12] Air-assisted dissection is safe, easy, and cheap method for removing the pterygium head from the corneal surface, which also facilitates the establishment of a clear and smooth corneal surface.

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.[13] Initially used by Tan et al, to reconstruct the bulbar conjunctival surface after excision of an extensive nevus, it facilitates early postoperative epithelialization and recovery with minimum postoperative inflammation and quick ocular rehabilitation and may aid in preventing serious complications associated with simple denuded HAM transplantation, such as scleral necrosis and secondary infection. Subsequently, the efficacy of this approach was studied in the management of pterygium surgery and a recurrence rate of 23% was noted.[13]

International Journal Dental and Medical Sciences Research
Volume 4, Issue 1, Jan-Feb 2022 pp 505-510 www.ijdmsrjournal.com ISSN: 2582-6018

NON SURGICAL TREATMENT: TOPICAL DIPYRIDAMOLE

Dipyridamole was originally introduced in 1959 as an antianginal medication and was subsequently found to inhibit platelet aggregation. Dipyridamole has also been shown to possess effects that are potentially quite relevant to pterygia. One of those effects is anti-inflammatory activity. A recent study attributed its anti-inflammatory effects to the suppression of TNF-α and PMA-mediated MMP-9 expression and interference with NF-β signaling and p38 MAPK activation.[14] Furthermore, it possesses antineoplastic properties, and additionally has been found to possess antiviral properties that could address the theorized association between conjunctival HPV and pterygia. Dipyridamole's anti-inflammatory, antiviral, antiproliferative, and (at low doses) antioxidant properties make it a novel prospective candidate to address the apparent multifaceted etiology of pterygia.

ADJUNCTIVE THERAPIES IN PTERYGIUM MANAGEMENT:

The high recurrence rates associated with surgery continue to be a problem, and thus adjunctive medical therapies have been incorporated into the management of pterygia. Studies have shown that recurrence rates have dropped considerably with the addition of these therapies; however, they are with their own complications.

Mitomycin C (MMC): MMC is an alkylating agent which inhibits DNA synthesis. By inhibiting DNA synthesis, it leads to the death of cells caused by the inability to repair the genotoxic injury caused by alkylation.[15,16] It can be used before, during or after pterygium surgery applied locally or in the form of eye drops. The injection application directly on the pterygium has the advantage of protecting the corneal endothelium and epithelium. Subconjunctival injection allows a more precise dose to be applied to the patient's eye, which usually does not occur with MMC application when using sponges directly on the sclera during surgery. Its action in the prevention of pterygium recurrence occurs by inhibition of fibroblast proliferation in the episclera region. The increased concentration and duration of the application may be associated with complications such as necrotizing scleritis, scleral calcification, ulceration, corneal edema, iritis, glaucoma, cataract, hypotony by injury of the ciliary body and damage to the corneal epithelium and endothelium.

Beta-irradiation (strontium 90): Irradiation has been used for the treatment of pterygium since the early 1950s and has been shown to reduce the recurrence rate after pterygium surgery to 1.7–12%.[17] The optimal total dosage of beta irradiation is between 10 and 30 Gy given at the time of surgery or within a few days after surgery. While beta irradiation reduces the recurrence rate of pterygium, significant long term complications, such as scleral necrosis and secondary infections, have been reported. It has now been replaced by other safer adjuvants.

Cytotoxic drugs: 5-fluorouracil, doxorubicine and daunorubicine also inhibits the proliferation of fibroblasts, but through different mechanisms involving the inhibition of thymidylate synthetase and other enzymes related to nucleic acid biosynthesis.

Loteprednol etabonate: It is a highly lipophilic corticosteroid, which facilitates its easy penetration through cell membranes. In a pilot study, the treatment of pterygium patients with LE twice daily (BID) for 14 days led to an approximate 50% increase in glucocorticoid receptor migration to the cell nucleus in the pterygium head tissue, as demonstrated using Western blot analysis of biopsied pterygium tissue, suggesting that perioperative treatment with topical LE could result in favorable clinical outcomes in pterygium removal.[18]

Insertion of multimicroporous expanded e-PTFE: Expanded polytetrafluoroethylene (e-PTFE), widely known as Gore-Tex, is a fluoropolymer that has been used in a range of surgical devices and demonstrates well established biocompatibility and biostability.[19] e-PTFE's hydrophobicity can prevent the wound area from postoperatively adhering to adjacent tissues. Previous studies have shown that e-PTFE can promote epithelialisation, inciting little inflammatory response and prevent recurrence of symblepharon in cicatricial ocular surface diseases. Current approach for managing recurrent pterygia is to perform a pterygial excision with intraoperative insertion of multimicroporous e-PTFE into the subconjunctival space at the nasal caruncle. Specifically, multiple micropores in the e-PTFE are created to enable the passage of oxygen from the air to the surgical wound in order to prevent hypoxia-induced scar formation during the initial proliferative phase of wound healing.

Antibiotics: Oral doxycycline, topical azithromycine etc can be a useful adjunct due to their beneficial nonantimicrobial effects, including anti-inflammatory, anticollagenase, meibomian lipid viscosity reduction, vascular stabilization, and anti-MMP 9 activities.

Topical bevacizumab: Topical bevacizumab drops have also been advocated in the control of corneal and conjunctival neovascularization. This often enables a significant therapeutic antineovascular effect in the cornea and conjunctiva – superficial vessels remain more susceptible to all therapeutic efforts, while deeper interstitial vessels prove more recalcitrant.[20]

GENE TARGETED FUNDAMENTAL THERAPY:

CRISPR-Cas9 system: Identification of molecular/genetic biomarkers of recurrence as well as patient- indivisualised therapeutic methods, in order to maximize therapeutic effectiveness will overcome the complicated problems in pterygium. The CRISPR-Cas9 system or "gene scissors" is cautiously predicted to be a therapeutic option in pterygium using gene-targeted fundamental techniques.[21]

APR-246/PRIMA-1^{Met}: Recent analyses suggest the occurrence of alterations and mutations in critical regulatory processes such as the S100 proteins, MAPK signal pathway, p53, or ras oncogenes in pterygium, which are associated with neoplastic conditions.[22] Inhibition of these underlying molecular mechanisms represents a possible approach for future medical treatments of pterygium, which could further reduce recurrence with the use as adjuvants or eventually even replace surgical treatment. APR-246/PRIMA-1^{Met} a small molecule, inhibits and reverses squamous metaplasia in human conjunctival epithelium and is capable of restoring the sequence-specific DNA-binding and transcriptional transactivation by mutant p53 in tumor cells.

REFERENCES:

[1]. The American Academy of Ophthalmology- management of pterygium.
[2]. Ophthalmology, International Edition 4th Edition- Myron Yanoff & Jay S. Duker
[3]. Kanski's Clinical Ophthalmology- a Systemic Approach 8th edition- Brad Bowling
[4]. Hirst L. W. Prospective Study of Primary Pterygium Surgery using Pterygium Extended Removal Followed by Extended Conjunctival Transplantation. Ophthalmology 2008; 115:1663–72.
[5]. Leonard P.K. Ang, Jocelyn L.L. Chua and Donald T.H. Tan.- Current concepts and techniques in pterygium treatment. Current Opinion in Ophthalmology 2007; 18:308-13.
[6]. Cho C. H., Lee S. B. Biodegradable collagen matrix (Ologen^{TM}) implant and conjunctival autograft for scleral necrosis after pterygium excision: two case reports. BMC Ophthalmology. 2015;15(1):p. 140. doi: 10.1186/s12886-015-0130-z.
[7]. Ang LP, Chua JL, Tan DT. Current concepts and techniques in pterygium treatment. Curr Opin Ophthalmol. 2007;18(4):308–313.
[8]. Hardten DR. Fibrin tissue adhesive. In: Hovanesian JA, editor. Pterygium: Techniques and Technologies for Surgical Success. Thorofare, NJ: Slack Incorporated; 2012:49–54.
[9]. Mitra S et al. Autoblood as Tissue Adhesive for Conjunctival Autograft Fixation in Pterygium Surgery. Poster presented at the Annual Meeting of the American Academy of Ophthalmology; Oct. 22 and 23, 2011; Orlando, Fla.
[10]. Bradley JC- Cautery fixation for amniotic membrane transplant in pterygium surgery. Cornea2011;30:194–5.
[11]. Bozkir N, Yilmaz S, Maden A. Minimally invasive pterygium surgery: a new approach for prevention of recurrence. Eur J Ophthalmol 2008; 18:27-31.
[12]. Gulkilik G, Kocabora S, Taskapili M, Ozsutcu M. A new technique for pterygium excision: air-assisted dissection. Ophthalmologica 2006; 220:307-310.
[13]. Ang, L.P.K., Tan, D.T.H., Phan, T.T., Li, J., Beuerman, R.W., Lavker, R.M. The in vitro and in vivo proliferative capacity of serum-free cultivated human conjunctival epithelial cells. Curr Eye Res. 2004;28:307–317.
[14]. Pterygium: nonsurgical treatment using topical dipyridamole - a case report- Case Rep Ophthalmol. 2014 Jan-Apr;5(1): 98-103
[15]. Raiskup F, Solomon A, Landau D, Ilsar M, Frucht-Pery J. Mitomycin C for pterygium: long term evaluation. Br J Ophthalmol. 2004;88(11):1425–1428.
[16]. Mastropasqua L, Carpineto P, Ciancaglini M, Enrico Gallenga P. Long term results of intraoperative mitomycin C in the treatment of recurrent pterygium. Br J Ophthalmol. 1996;80(4):288–291.
[17]. Postoperative beta irradiation for control of pterygium- Smith RA, et al. -J Miss State Med Assoc. 2001
[18]. An update on the surgical management of pterygium and the role of loteprednol etabonate ointment- Clin Ophthalmol. 2014; 8: 1105-1118.
[19]. Management of complicated multirecurrent pterygia using multimicroporous expanded

polytetrafluoroethylene – British Journal of Ophthalmology- Volume 97, Issue 6

[20]. Kim SW, Ha BJ, Kim EK, Tchah H, Kim TI. The effect of topical bevacizumab on corneal neovascularization. Ophthalmology. 2008 Jun; 115(6):e33-8.

[21]. Current approaches and future directions in the management of pterygium- Ind J Ophthalmol. 2018; 11(5): 709-711.

[22]. APR-246/PRIMA-1Met Inhibits and Reverses Squamous Metaplasia in Human Conjunctival Epithelium- 2016 Feb;57(2):444-52. doi: 10.1167/iovs.15-17519.