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Review Article

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Treatment of pterygium

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Abstract

The treatment of ocular pterygium has been subjected to the development and application of various new strategies in the last few years. The worrisome problem of recurrence seems to have been significantly reduced with the newer methods of treatment. The field is however, still evolving. This review sets out to examine the various newer approaches to treating pterygium and in spite of the recent developments, to highlight the remaining challenges thereby suggesting the possible direction of future research. Also, to suggest treatment options for Ophthalmologists working in environments with limited resources.

A library search and Internet search of PubMed and Google was conducted in 2010. Search terms included "pterygium in combination with surgery", "radiotherapy", "chemotherapy", "graft", and "recurrence." Abstracts were reviewed and relevant articles especially those published from the year 2000 to date were given more attention and when possible, reviewed in full. The relevant references in such articles were also reviewed.

In conclusion, excision and adjunctive treatment with mitomycin C or conjunctival autograft is the most acceptable and most popular mode of treating both primary and recurrent pterygium. Outcomes seem to have been further improved with adjuvant combination therapy and the introduction of newer approaches to treatment.

Keywords: Adjuvant treatment, excision, pterygium, recurrence, review

Résumé

Le traitement des Ptérygion oculaire a été soumis à l'élaboration et l'application des diverses stratégies de nouveau au cours des dernières années. Le problème inquiétant de récurrence semble ont été significativement réduits avec les nouvelles méthodes de traitement. Le champ est cependant toujours en évolution. Cette revue vise à examiner les diverses approches plus récents à traiter les ptérygium et en dépit de l'évolution récente, de mettre en évidence les défis restants, suggérant ainsi l'orientation possible des recherches futures. Aussi, pour suggérer de traitement des options pour les ophtalmologistes travaillant dans des environnements avec des ressources limitées. Une recherche de la Bibliothèque et l'Internet recherche de Pub Med et Google a été réalisée en 2010. Les termes de recherche inclus « Ptérygion en combinaison avec la chirurgie esthétique », « radiothérapie », « chimiothérapie », « greffon » et « récurrence. » Résumés ont été examinés et des articles pertinents, notamment ceux publiés depuis l'an 2000 à ce jour ont donné plus d'attention et dans la mesure du possible, examiné au complet. Les références pertinentes dans ces articles ont également été examinés. En conclusion, l'excision et traitement d'appoint avec mitomycine c ou autogreffe conjonctival est le mode plus acceptable et plus populaires de traitement primaire et récurrente Ptérygion. Résultats semblent ont été améliorées avec polythérapie adjuvant et l'introduction de nouvelles approches de traitement.

Mots clés: Traitement adjuvant, l'Excision, ptérygium, récurrence, examen

Introduction

Pterygium, an eye condition common in tropical regions, is a benign wing shaped fibrovascular conjunctival growth. While the body of the pterygium remains on the sclera, the head advances unto the cornea in many cases affecting vision, causing general discomfort, and becoming a cosmetic

nuisance. Various theories have been postulated on the aetiopathogenesis[1,2] and its predominantly nasal location on the eye.[3] Exposure to ultraviolet light (UVB) is generally believed to be a strong risk factor for the development of pterygium.[4]

The main method of treating a pterygium is by surgical excision. Any conservative treatment is mainly symptomatic and temporary usually for the early stages of the disease. Conservative treatment involves the use of artificial tears or non-preserved lubricant eye ointment so as to provide comfort and relief from foreign body sensation. Short term anti inflammatory eye drops may also be useful for inflamed pterygia. The indications for surgical excision include a disturbance of visual function, significant discomfort, and cosmetic reasons. The complete excision of a pterygium from the cornea and sclera, subsequently leaving a bare denuded corneoscleral surface is the classical surgical procedure. This procedure, also known as the bare sclera technique, was first fully described by D`Ombrain in 1948.[5] For sometime, this has been the treatment of choice for pterygia but the high frequency of recurrence associated with this procedure has led to the search for adjunctive treatment options. Other uncommon and more easily managed complications of pterygium excision include corneal epithelial defects, dellen formation, and pyogenic granuloma. The rare complications of symblepharon and diplopia may be associated with the excision of multirecurrent pterygia. Risk factors for the recurrence phenomena of pterygia are not distinctively known but there is a higher risk of recurrence after re-excision of a recurrent pterygium compared to a primary pterygium. The bare sclera technique has a reported pterygium recurrence rate of between 30 and 90%.[6-8] There is no standard definition of recurrence but it is generally accepted that there is a recurrence when a fibrovascular growth in the position of the previously excised pterygium crosses the limbus unto the cornea for any distance. At least 97% of all recurrent pterygia manifest within the first year after excision.[9]

Pterygium Excision

The objective of surgical excision is to completely remove the head, neck, and body of the pterygium. To achieve this, at least two main methods with different variations are in use. After adequate local anesthesia, the first approach involves grasping the head of the pterygium with forceps and separating it from the cornea using a surgical blade. The neck and body of the pterygium are then dissected with Westcott scissors posteriorly up to about four to six millimeters from the limbus and then excised. The second approach is to use the scissors to undermine and dissect below the body of the pterygium. A bluntedged instrument such as an iris repositor is then inserted under the body of the pterygium and while pulling on the body with forceps to form a tent; the head is sliced off the cornea by a sawing motion of the iris repositor (avulsion technique). For both approaches, any pterygium tissue remnants on the cornea are gently scraped off with the surgical blade until a clear corneal bed is obtained. Any encountered bleeding points are gently cauterized. Argon laser and the excimer "laser blade" have been used in pterygium excision with varying degrees of success.[10,11] They are used to either fully excise the pterygium, or to smoothen the corneal surface after surgical excision. The main problems encountered during surgical excision include getting a good separation plane during blunt dissection, and the persistence of pterygium tissue remnants on the cornea. These problems seem to have been recently addressed by the introduction of the use of alcohol on the cornea prior to pterygium surgical excision.[12] Ethanol splits the basement membrane and destroys hemidesmosome junctions between corneal epithelial cells. It has been in use for long in corneal refractive surgery. Unlike with blunt dissection, prior alcohol application creates a smoother and clearer separation plane. The pterygium head is easily and completely scraped off with a blunt spatula from the underlying cornea. This could be a method of choice for patients in whom excellent vision in the immediate postoperative period is critical or in treating some recurrent pterygia where the cornea has become thinner and more delicate. Prospective clinical trials are now ongoing to determine the efficacy of ethanol -assisted pterygium excision. Despite the various methods of pterygium surgical excision, there is yet no definitive evidence to show that outcome is influenced by the excision technique.

Adjuvant Therapy

Due to the high recurrence rate associated with the bare sclera technique, it is now generally no more accepted as the sole treatment for pterygium. Consequently, various methods and procedures used in the management of the bare sclera have evolved. These include further surgical/grafting procedures, chemotherapy, and the use of radiotherapy. The availability of a variety of modalities makes it possible to use another method when one fails. It also allows for a combination of methods such as chemotherapy and grafting in difficult or multi recurrent cases of pterygium.

The use of the various adjunctive therapies has in turn introduced new additional concerns regarding aspects such as safety, cost of surgery, duration of

surgery, immediate postoperative cosmesis, and patient comfort. There is also the yet undocumented but potential threat of infection associated with the foreign materials (tissue glue and amniotic membrane) that could be used in treatment. A general concern about avoiding eye-threatening complications while treating an essentially benign condition is also a consideration.

Radiotherapy

Postoperative beta irradiation applied to the bare sclera is a relatively safe and effective adjuvant treatment for pterygium. It has been in use for decades and has led to a satisfactory reduction of the recurrence associated with the bare sclera technique.[13-15] Usually, it is applied as a single post operative dose (2500 to 3500 rads), irradiation should be applied within 24 hours of pterygium excision or better still, on the surgical table for best results.[16,17] As adjuvant therapy, irradiation is usually given alone but could be combined with other adjuvant treatment such as a graft applied over the bare sclera. This treatment combination has been successfully applied on complicated and multi recurrent pterygia.[18] However, because of the increased risk of complications such as scleral melting, irradiation should not be combined with adjuvant chemotherapeutic agents such as Mitomycin C (MMC). In fact drugs with radiomimetic actions such as MMC should be avoided in treating the recurrent pterygia of previously irradiated eyes. Complications of beta irradiation are few but some could be long term and sight threatening especially in the past when higher total doses of radiation were used. Documented complications of radiotherapy include conjunctival inflammation, corneal opacities, scleritis, cataract, uveitis, corneal/scleral thinning, globe perforation, and endophthalmitis.[13-15,19] These potential complications, relative higher cost, and the added inconvenience of arranging for treatment application, have made radiotherapy quite unpopular among surgeons despite its long presence and history of effective usage.[20]

Chemotherapy

Over the years, various chemotherapeutic agents have been used in the treatment of pterygium. All were applied as adjuvant therapy with the aim of preventing recurrence. Triethylene thiophosphoramide (thiothepa)[21,22] applied topically as eye drops, was one of the earliest used but has now largely been abandoned mainly because of the skin depigmentation and eyelash poliosis associated with its use. Other drugs that have been used though on a limited scale include doxorubicin[23] and long-acting depot steroids. The steroids were usually administered in combination with other adjuvant drugs[24] or surgical graft[25] in order to improve the outcome of surgery. More recently, alcohol (ethanol) and anti-vascular endothelial growth factors (anti-VEGF) have been introduced. Alcohol causes a denaturation of enzymes, cytokines, and growth factors involved in pterygium formation and recurrence. Chen and Hsu[12] used 20% ethanol on 38 eyes of patients with primary pterygia both on the cornea to assist pterygium excision and also on the bare sclera as adjuvant therapy to prevent recurrence. In comparison to 40 eyes with primary pterygia in whom low dose MMC was applied to the bare sclera, the ethanol group had fewer recurrences (5.3%) and generally fewer postoperative complications. As for anti-VEGF drugs, their use was encouraged by the higher levels of VEGF found in pterygium tissue compared to normal conjunctiva.[26] No definite role for anti VEGF drugs has been found but Wu and coworkers[27] in a case report suggested that by inhibiting neovascularisation, topical bevacizumab eyedrops (an anti-VEGF) could be effective in preventing recurrence in patients with impending recurrence after pterygium surgery. For impending pterygium recurrence, anti-VEGF could probably be a safer alternative to subconjunctival injections of MMC or fluorouracil. More work is required in evaluating efficacy and safety of the use of both ethanol and anti VEGF either alone or in combination with other adjuvant treatments.

Perhaps the most widely used adjuvant drugs are 5 fluorouracil (5FU) and MMC. Of the two, MMC has become more widely used and accepted. This may not be unconnected to the stronger antiproliferative effect shown by MMC as a result of its cytotoxic action on both fibroblasts and vascular endothelial cells unlike 5FU whose action is mainly on fibroblasts.[28] Maldonado[29] in 1995 suggested that low dose (0.1%) intraoperative 5FU had no beneficial role in preventing pterygium recurrence. Bekibele[30] and coworkers in 2004 after a retrospective non-randomized review, found beta irradiation to be marginally superior to 5FU in preventing recurrence. However, for reasons of cost, availability, and convenience, recommended the use of 5FU ahead of beta irradiation. The same author in another prospective comparative study[31] reported 5FU as marginally superior to conjunctival auto graft although sample size in this second study was relatively small. 5FU may therefore still have a place in the treatment of pterygium.

Mitomycin C

MMC is an antineoplastic antibiotic agent with radiomimetic effect. Its use in pterygium surgery was popularized by Singh[32] and has since been

found to result in lower recurrence rates when compared to the bare sclera technique. Reported recurrence rates range from 0 to 38%.[8,33-35]

MMC is applied either as a preoperative subpterygial injection, an intraoperative application, or as postoperative eye drops. A number of MMC doses (various concentrations) have been used for various durations but the intraoperative low dose 0.2 mg/ml (0.02%) concentration applied directly on the bare sclera over three to five minutes is now the most popular mode of administration.[20] This could serve as the sole treatment or an additional graft of conjunctiva or amniotic membrane may be applied to cover the bare sclera.[36] MMC intraoperative application in combination with a surgical graft could also be applied to the conjunctival fornix (not the bare sclera) to help restore the fornix after a symblepharolysis[37] and secondly, to help restore ocular motility after excision of multirecurrent pterygia.[38] On the other hand, postoperative application of MMC as eyedrops is usually applied two to four times daily over five to fourteen days. Both the intraoperative and postoperative methods of application have similar reported recurrence rates and similar risks of serious potential side effects.[39,40] The main advantage of single dose intraoperative administration has been the control it gives to the surgeon over usage of the drug thereby avoiding the possible problem of poor patient compliance. Recently, concerns over the effect of intraoperative application on the corneal endothelium have been raised.[41] However, some studies have shown that changes in or loss of corneal endothelial cells does not occur when low dose MMC is applied for a short duration of one minute[42] or when applied before removal of the pterygium head from the cornea.[43] These were all short-term studies of less than four months follow-up duration, hence long-term assessments of the corneal endothelium after MMC treatment will be required.

Apart from the potential long-term effects on the cornea, use of MMC like with radiotherapy has been associated with serious complications that could present long after the surgery.[39,44] Although said to be uncommon, these serious complications are sight threatening and may include scleral melting leading to perforation, uveitis, infectious scleritis, and endophthalmitis. Prior to use, all patients must be counseled on the potential risk of complications. MMC is better avoided in patients with tear deficiency, ocular surface disorders, icthiosis, rosacae, and patients with systemic diseases associated with scleritis/episcleritis. In such patients, alternative surgical options should be considered.

Adjuvant Surgery

Surgery could be the sole adjunct or could be combined with radiotherapy or chemotherapy especially for multi recurrent pterygia. Applicable surgical procedures include lamellar keratoplasty, amniotic membrane transplantation (AMT), and conjunctival grafting including all its variants. These various surgical options could in turn also be applied alone or in combination. For conjunctival grafting and AMT, attachment of the graft could be either by sutures or fibrin tissue glue,[45] however, the fibrin glue (Tisseel, Baxter corporation, Canada) is now generally preferred over sutures. Use of fibrin glue reduces both the operation time and postoperative discomfort experienced by the patient. In a prospective comparative study by Karalezli,[46] the average duration of surgery using fibrin glue was 15.7 minutes compared to 32.5 minutes for sutures. Studies[47,48] have also shown that it reduces the postoperative inflammation and pterygium recurrence rate compared to sutures. It has also been shown by histological examination to be safe on ocular tissues[49] causing no complications and in the rare event of graft dehiscence, fibrin glue could be reapplied. There is, however, the potential but yet undocumented risk of cross infection with its use and in resource poor settings, issues of added cost and availability of the glue become important.

Lamellar keratoplasty

It is mainly indicated for recurrent pterygia in the presence of thinned or scarred corneal tissue. A significant number of patients undergoing this procedure, experience a postoperative reduction in visual acuity.[50] The procedure requires donor corneal tissue with the associated risks of graft rejection and transmission of infection. Corneal banking and keratoplasty services are not well established in many African countries. Compared to other adjunctive procedures, keratoplasty is technically more difficult to perform.

Amniotic membrane transplantation

Human amniotic membrane is presumed to suppress inflammation and formation of fibrovascular tissues and has been used with success to cover the bare sclera after pterygium excision. It serves a useful alternative to conjunctival tissue in situations where there is a large conjunctival defect and shortage of healthy conjunctival tissue to cover the bare sclera commonly seen in multi recurrent pterygia. AMT is especially useful in patients that have undergone previous conjunctival autografting and in those with glaucoma with a need to preserve conjunctiva for potential future use. In comparison to keratoplasty, amniotic membrane unlike donor cornea has no human leucocyte antigens and therefore carries no risk of rejection but like donor cornea, there is need to screen for infections. Human amniotic

membrane though more readily donated than cornea is still not commonly available in most African countries and will have to be purchased from other countries thereby adding to the cost of surgery. This is as a result of the present paucity of tissue banks on the continent. The advantages of AMT over conjunctival grafting include a shorter surgical time, less pain and faster recovery (since no donor site is injured), and a generally better cosmetic outcome in the immediate postoperative period.[51] However, in terms of preventing pterygium recurrence, most studies[51-53] have shown that it is not as effective as conjunctival grafting and have documented recurrence rates above 10% using AMT alone. The reported novel use of an ex-vivo expanded conjunctival epithelial sheet on an amniotic membrane substrate has only aided early postoperative ocular surface re-epitheliazation compared to routine AMT but did not significantly change the recurrence rate.[54] However, the effectiveness of AMT could be improved by the use of fibrin glue instead of sutures, or by carrying out a more extensive removal of subconjunctival fibrous tissue during pterygium excision followed by an injection of a long acting steroid. Solomon *et al*.[55] reported a lower recurrence rate of 3.0% for primary and recurrent pterygia using this approach. Ma *et al*.[56] showed that combining AMT and intraoperative MMC seems to improve the outcome in primary pterygium surgery but not for recurrent pterygia, where the combination did not significantly change recurrence rate.

Conjunctival autograft

Since its introduction by Kenyon *et al*.[57] in 1985, conjunctival autograft has gradually come to be a popular treatment for pterygium. Covering the bare sclera by using autologous conjunctival tissue could be performed by a primary direct closure, a sliding conjunctival flap,[58,59] or by a free conjunctival autograft.[57] The free graft is typically harvested from the superior bulbar conjunctiva and sutured or more preferably, glued to the bare sclera defect after pterygium excision. The sliding and free grafts seem to be equally effective but direct conjunctival closure alone is not as effective as either the sliding or free graft.[36] Although more time consuming and technically demanding, conjunctival autografting is safer and probably more effective than radiotherapy or chemotherapy since it is free of any serious side effects. Recurrence rates are essentially similar to those seen after the use of MMC or beta irradiation. Reported recurrence after conjunctival autograft range from 0 to 39%.[20,60,61] This figure range should now expectedly reduce since it was mainly based on studies carried out before the advent of fibrin glue and alcohol assisted pterygium excision. Most of the studies[12,46,48] that now apply these new techniques report a single unit recurrence rate. Other factors contributing to the wide variation in recurrence rates seen with conjunctival grafts could be related to the differences in surgical techniques and experience among surgeons. Generally, graft success is enhanced by among other things, the use of minimal cautery, ensuring the graft is tenon free, removal of excess fibrin glue, and countering post operative graft retraction by using a slightly oversized (by 1 mm) graft. Additional use of intraoperative MMC with the conjunctival graft seems to improve success rates. Two studies support this impression. The first study by Frucht-Pery and coworkers[62] had a 0% recurrence with MMC and conjunctival graft combination compared to a 13.3% recurrence rate with conjunctival autograft alone. Katircioglu *et al*.[63] in the second study also reported a 0% recurrence with MMC and conjunctival graft combination compared to a 16% recurrence rate with the graft alone. However, another non-comparative study by Young *et al*.[64] reported a recurrence rate of 3% with the MMC/conjunctival graft combination. Additional radiotherapy on the other hand, does not seem to be very useful as Amano *et al*.[65] found MMC plus conjunctival autograft to be more effective than beta irradiation plus conjunctival autograft.

Variants of the free conjunctival autograft[66] include autorotation of the graft, narrow strip juxta limbal grafting leaving a posterior bare sclera zone, and a limbal-conjunctival graft, which includes about two millimeters of limbal tissue in the graft. The limbal-conjunctiva graft aims to replenish damaged limbal stem cells with fresh tissue in order to reduce the tendency for recurrence. In terms of preventing recurrence, none of these variants could be said to conclusively offer any additional advantage over the free or sliding autograft.[67-69] But in fact limbal-conjunctival autograft is technically more tasking and increases surgical time in addition to the possibility of limbal tissue damage to the donor site.

Conclusion

Direct comparisons between studies is made difficult for various reasons some of which include a wide range of sample sizes, whether primary or recurrent pterygia under study, additional intervention in some cases of early recurrence, and the differences in the definition of pterygium recurrence and follow-up periods. These reasons contribute to the varied and sometimes conflicting results observed between studies. Regarding pterygium excision, there is presently no agreement on the best method of excision and excision alone without adjuvant treatment is now no longer acceptable. The various adjuvant therapies and

combination of adjuvant therapy have served to significantly improve treatment outcomes in terms of recurrence, cosmesis, and patient satisfaction. Of the adjuvant therapies, MMC and conjunctival autograft are the most popular and give the most satisfactory results. Of these two, conjunctival autograft is preferred because of long-term safety concerns. In this regard, ethanol with its preliminary good safety profile seems a promising alternative to MMC and therefore is deserving of further investigation and interest. Other areas requiring further attention include identification of factors responsible for recurrence and the formulation of standard guidelines on the best treatment approach for the different types of pterygium. At the present state and as first line treatment, it would seem reasonable for ophthalmologists working in resource limited settings to use adjuvant chemotherapy such as MMC or 5FU and in some cases with additional depot steroid as treatment for primary pterygium. But for recurrent pterygia, a combination of conjunctival autograft plus MMC could be used.

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