Pterygium: an update on pathophysiology, clinical features, and management

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***Abstract*:** Pterygium is a relatively common ocular surface disease. The clinical aspects and the treatment options have been studied since many years ago, but many uncertainties still exist. The core pathologic pathway and the role of heredity in the development of pterygium are still attractive fields for the researchers. The role of pterygium in corneal irregularities, in addition to the refractive properties of pterygium removal, has been increasingly recognized through numerous studies. The association between pterygium and ocular surface neoplasia is challenging the traditional beliefs regarding the safe profile of the disease. The need for a comprehensive clinical classification system has encouraged homogenization of trials and prediction of the recurrence rate of the pterygium following surgical removal. Evolving surgical methods have been associated with some complications, whose diagnosis and management are necessary for ophthalmic surgeons. According to the review, the main risk factor of pterygium progression remains to be the ultraviolet exposure. A major part of the clinical evaluation should consist of differentiating between typical and atypical pterygia, where the latter may be associated with the risk of ocular surface neoplasia. The effect of pterygium on astigmatism and the aberrations of the cornea may evoke the need for an early removal with a purpose of reducing secondary refractive error. Among the surgical methods, conjunctival or conjunctival-limbal autografting seems to be the first choice for ophthalmic surgeons because the recurrence rate following the procedure has been reported to be lower, compared with other procedures. The use of adjuvant options is supported in the literature, where intraoperative and postoperative mitomycin C has been the adjuvant treatment of choice. The efficacy and safety of anti–vascular endothelial growth factor agents and cyclosporine have been postulated; however, their exact role in the treatment of the pterygium requires further studies.

Keywords: adjuvant therapy, complications, pathophysiology, pterygium, surgical removal

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Background

Pterygium (also known as surfer's eye) is an ocular surface disease characterized mainly by a wing-shaped growth of limbal and conjunctival tissue over the adjacent cornea. As a result of alterations in local ocular surface homeostasis, the main components of pterygium include proliferative clusters of limbal stem cells (LSCs), epithelial metaplasia, active fibrovascular tissue, inflammation, and disruption of Bowman's layer along the invading apex of the pterygium.[1] As the experimental models have failed to induce pterygium formation in animals, it seems that pterygium is an ocular disease only observed in humans.[2] Although it is a well-known ocular condition since many years ago, numerous studies performed on pathophysiology and management of pterygium have never dissolved some main uncertainties about this common ocular surface disease.

This review provides a major review on etiologies, risk factors, complications, and surgical management of pterygium, focusing on the updates and the new features of the literature. A literature review was performed based on the results yielded from searching PubMed, Embase, Web of Science, Scopus, and Cochrane database using the following keywords: pterygium, complications, etiologies, pathophysiology, classification, and treatment.

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Articles published in English from 1948 to 2020 were analyzed and included in this review.

Epidemiology

Depending on the population studies, the prevalence of pterygium lies within the range of 1% to more than 30%.[3–7] According to a meta-analysis of 20 studies published in 2015, the pooled prevalence of pterygium is around 10%.[8] The maximum prevalence rate for pterygium has been reported in a Chinese study on rural population, where a rate of 33% was yielded.[9]

Some reported risk factors for pterygium are age,[3,4] male sex,[10,11] experience of outdoor job,[3,12] low education,[5] rural residence,[11] low income,[5] darker skin complexion,[3] and smoking.[5] In a North American study, the prevalence of pterygium was reported to be 2.5–3 times higher in Black population compared with Whites.[3] Despite its worldwide distribution, pterygium is the most common in geographic latitude 40° around the equator.[13] The prevalence rate of pterygium within this area is reported to be more than 10 times higher than that outside it,[14] which strongly supports the role of ultraviolet (UV) irradiation in the pathogenesis of pterygium.

Histopathology

Pterygium epithelial cells

The main histologic findings in a pterygium specimen from surface to depth include invading pterygium epithelial cells with proliferative features, squamous metaplasia, hyperplasia of goblet cells, underlying disrupted Bowman's layer, stromal fibroblasts and vessels, altered extracellular matrix (ECM) with accumulation of collagen and elastin fibers, and inflammatory infiltration.

Over a century ago, Fuchs described clusters of small primitive cells in the basal epithelia of pterygium,[15] which was visualized later by slit-lamp and confocal microscopy.[16] Named as Fuchs' flecks, these clusters were revealed by Dushku and colleagues[17,18] to alter limbal epithelial basal cells with migratory features which are involved in the initiation of pterygium pathogenesis. These abnormal LSCs are known as pterygium cells and have been investigated in several studies.

Discovery of pterygium cells and their migratory and proliferative capabilities has revolutionized the traditional beliefs regarding the pathogenesis of pterygium. For a long time, pterygium progression was considered to be the result of two consecutive events in limbal area: (1) primary disruption of limbal barrier due to chronic UV exposure, and (2) and subsequent extensive proliferation of conjunctival tissue, blood vessels, and inflammatory cells over adjacent cornea through an active process called conjunctivalization.[19] It was believed that the process of conjunctivalization takes place over the full length of invading pterygium tissue, from head to body. However, the findings of further studies were not consistent with earlier impressions. Bai and colleagues[20] demonstrated a spatial presence of proliferating stem cells over the pterygium tissue. It was revealed that epithelial cells with proliferative markers such as p63 and CK15 are located over the head of the pterygium, while the region over the limbus lacks these factors. Also, PAX6 was reported to be predominant in the head region, and matrix metalloproteinase (MMP) 2 and 9 were located only over the head margin.[20] These topographical data demonstrated the migratory front and proliferative capacity of LSCs located in the head of the pterygium, which acts as a proliferative battery for progressive growth and as a migratory force via MMP-induced degradation of ECM. According to this spatial divergence, now it is believed that the head of the pterygium with its altered LSCs is responsible for the pathogenesis of the pterygium, and pathologic events may not be justified only by limbal barrier defect and conjunctivalization.[20] The critical factor for the initiation of pterygium is a limbal reorganization through the formation of pterygium cells, rather than a simple limbal failure. This reorganization is supposed to be associated with UV-induced damages or genetic susceptibilities. Some studies have investigated atypia in pterygium epithelial cells. Gaton and colleagues[22] found only mild dysplasia in about 6% of their cases.[21] In another study, mild atypia was discovered in more than 50% of pterygium specimen. Despite different rates of atypia, it seems that reports concur with each other that the atypia of pterygium cells figures around mild stage.

Beyond the pterygium cells, the cytology of superficial cell population in pterygium specimen has revealed a unique feature of the pterygium surface: squamous metaplasia associated with an increased population of goblet cells.[23]

Squamous metaplasia is the consequence of a wide variety of ocular surface diseases, including dry eye syndrome and vitamin A deficiency.[24] It is

characterized by stratification of the epithelial cells in association with abnormal keratinization. In cellular level, squamous metaplasia is manifested by flattening and enlargement of superficial epithelial cells and pyknotic changes of cellular nuclei.[24] Squamous metaplasia has been reported to be present in more than 70% of pterygium cases,[23] and it has made some authors to propose an association between pterygium and dry eye syndrome.[25,26] These authors believe that unstable tear film plays a critical role in the pathogenesis of pterygium. In addition to squamous changes, an increased density and abundant distribution of goblet cells have been reported in histological studies.[23,27] This is a unique feature of the ocular surface in pterygium, because squamous metaplasia is usually expected to be associated with reduced number of goblet cells. It is notable that in a recent study, more than 80% of cases showed epithelial hyperplasia; however, goblet cell hyperplasia was less frequent than previously reported; only 31.9% of the cases had goblet cells hyperplasia.[22]

Although it can be the result of abnormal distribution of tear film over an elevated surface, squamous metaplasia is seen throughout the bulbar conjunctiva in a graded fashion, where it is most severe over the pterygium surface. Following the epithelium covering the pterygium, interpalpebral and inferior bulbar conjunctiva demonstrate the most severe squamous changes in the absence of clinical disease, and superior conjunctiva under the upper eyelid (where it can be protected from UV radiation) shows the least changes of surface epithelium. Diffuse squamous metaplasia with graded series over bulbar conjunctiva, defected apoptosis process in conjunctival epithelial cells, and increased density of goblet cell are all consistent with the hypothesis that pterygium is a diffuse disease of ocular surface epithelium.

Another feature observed in approximately 50% of cases is the pigmentation of epithelium.[22] The presence of pigment deposits can be justified by the exposure to UV light.

Pterygium stroma

Solar basophilic elastoid degeneration is observed in the pterygium stroma in all cases.[22] The presence of stromal vessels is both a cosmetic issue and a therapeutic target in the management of pterygium. These vessels are associated with stromal fibrosis, where the vascularity is usually more prominent than the fibrosis.[22] A mild chronic inflammatory response, either in the stroma or in the epithelium, has been reported in the majority of pterygium cases.[28,29]

Etiology and risk factors

Previous studies have indicated that numerous risk factors are associated with pterygium, including UV radiation,[30,31] environmental irritants such as dust and wind,[13] viral agents,[32,33] familial and hereditary factors,[34] and immunological and inflammatory factors.[35,36]

Other risk factors suggested by recent studies may include the transcription factors cAMP response element–binding protein,[37] phospholipase D,[38] cytochrome P450 1A1 protein,[39] and aquaporin-1 and aquaporin-3.[40] Despite of our recent expanding knowledge about the role of different factors in the pathogenesis of pterygium, sunlight exposure remains to be the most important risk factor for the initiation and progression of pterygium.

Ultraviolet exposure

The association between development of pterygium and UV radiation can be concluded from numerous epidemiological studies.[41] The "pterygium zone" has been described as the area between 40° north and south of the equator, where a higher intensity of UV radiation influences the population of the region.[42] The similarity between histopathologic findings of UV-induced skin damage and pterygium supports the idea.[43] In addition, nasal predisposition of pterygium incidence is known to be correlated with an increase of more than 20-fold in irradiation of the nasal limbus, rendering the area more vulnerable for UV-induced injuries and development of pterygium.[13,44]

UVA and UVB are the primary subtypes of solar UV rays that reach the ocular surface. Although initial studies focused on the role of UVB in DNA damage and alteration of intracellular signaling in ocular surface disease, epidemiological studies have revealed that both UVB and UVA are associated with the development of pterygium. Through inducing reactive oxygen species, UVA causes indirect damage to DNA and activation of transcription factors, which regulate the expression of multiple genes involved in ECM changes.[45,46]

UV light can induce the development of pterygium through damaging limbal LSCs,[16,47] altering

the function of stromal fibroblasts,[17] or inducing inflammatory responses.[48] Among them, inflammatory responses may be of least importance.[49,50] A two-stage hypothesis has been proposed for the role of UV in pterygium development; initiation of the process relies on the damage of LSCs and formation of pterygium cells, and the progression is conducted by disrupted limbal barrier, upregulation of inflammatory cytokines, and production of growth factors and MMPs.[42]

At least for a decade, the main pathway of UV-induced LSC damage was believed to be p-53 mutations.[51] Reid and Dushku found abnormally high expression of p-53 protein in basal cells of pterygium epithelium and hypothesized that UV may cause p-53 mutations and consequent accumulation of p-53 protein in pterygium immunohistochemistry staining.[52] P-53 pathway is responsible for programmed cell death, and its deficiency results in the formation of altered LSCs which evolve into proliferative pterygium cells.[52] However, the hypothesis of p-53 mutations was criticized by further findings. Primarily, some studies failed to detect elevated levels of p-53 proteins in pterygium, weakening the necessity of p-53 mutations for pterygium cell formation.[53] Furthermore, some DNA sequencing analyses illustrated no mutation in p-53 genes in pterygium.[54] Also, through some molecular procedures, it was revealed that accumulation of p-53 proteins in a tissue may be secondary to normal exposure to sunlight, because UV can stabilize these proteins via post-transcriptional mechanisms.[55] This normal response to UV radiation can explain the accumulation of p-53 protein in initial studies. Accordingly, the exact role of p-53 in the development of pterygium cells remains to be elucidated, and this variability of p-53 expression may suggest that mutations in other tumor suppressor genes may be involved in the initiation of pterygium formation.[42]

UV exposure is also responsible for the abnormal behavior of pterygium fibroblasts. These fibroblasts have been revealed to possess more proliferative capacity, compared with normal conjunctival stromal cells.[17] They can form colonies in culture media, require less exogenous growth factor for activation, and are characterized by elongated nuclei and irregular nuclear pores in electron microscopy.[56,57] Three different pathways have been proposed for UV-induced activation of pterygium fibroblasts: (1) they can be damaged directly by UV radiation through multiple DNA alterations; (2) UV-altered LSCs may activate underlying fibroblasts through transforming growth factor-β (TGF-β) and fibroblast growth factor (b-FGF)-dependent mechanism;[52] or (3) conjunctival endothelial cell damage may alter the metabolism of stromal fibroblasts, which is manifested by alteration of collagen and elastin fiber expression.[58] Although UV radiation is believed to play the main role in the formation of pterygium fibroblasts, there are contrasting ideas regarding this issue.[59,60] These hypotheses may challenge the role of UV in the alterations of pterygium fibroblasts.

Finally, UV-induced inflammation and tissue remodeling is involved in the pathogenesis of pterygium. Multiple studies have reported higher levels of inflammatory cytokines, growth factors, and MMPs in pterygia.[43,61] In vitro experiments revealed that elevated expression of these factors in pterygium cells is inducible by UV radiation.[42] UV-mediated alterations of limbal stem cells induce the production of numerous inflammatory factors and MMPs, contributing to the inflammation, angiogenesis, and invasion of pterygium. Similarly, pterygium fibroblasts activated by UV produce high levels of growth factors and extracellular enzymes, which facilitate invasion of pterygium through ECM remodeling and dissolution of Bowman's layer.[42]

Heredity

For the first time in 1893, familial incidence of pterygia was reported by Gutierrez-Ponce, where five affected males were detected in three generations of a family.[62] Subsequent reports revealed high incidence of pterygium in certain families over numerous consecutive generations, suggesting the role of heredity factors in predisposing the conjunctiva to exacerbated reactions to environmental stimuli.[63–66] In these reports, various modes of inheritance, including autosomal dominant with reduced penetrance, polygenic, multifactorial, and non-Mendelian inheritance, have been described; monozygotic twins concordant have been proposed; and females are reported to be affected as often as males.[66–68]

Several familial genes and pathways have been proposed to be involved in the inheritance of pterygium. Familial defects in most of these pathways predispose affected individuals to an abnormal fibrovascular response to UV radiation.[34,69,70] As a candidate gene, MMP-1 has been proposed

to be involved in familial pterygium. It is believed that certain polymorphism of the MMP-1 promoter can predispose carriers to develop pterygia through a loss of heterozygosity process.[2] Polymorphism of proangiogenic genes has provided another field of interest in familial pterygium. As special polymorphisms of vascular endothelial growth factors (VEGFs) are associated with higher vascularity of the pterygium and variable response to anti-VEGF agents, it is proposed that variation of VEGF genes may explain the familial incidence of the disease.[71] MicroRNAs have also been implicated in the pathogenesis of pterygium. These are small noncoding RNAs that indirectly regulate special protein levels and gene expression. The presence of these molecules is related to anti-neoplastic properties in ocular tissues.[72] Recently, it has been revealed that microRNA-145 level is negatively correlated with more extensive and thick pterygia. In addition, reduced level of the microRNA has been detected in recurrent pterygium.[73,74] Accordingly, microRNAs may draw attention as they can serve as prognostic factors, therapeutic targets, and even the clue of pterygium inheritance. Other targets of genetic studies in pterygium inheritance are differentially expressed genes, including FN1, KPNB1, DDB1, NF2, BUB3, PRSS23, MEOX1, ABCA1, KRT6A, SSH1, RBM14, and UPK1B. These genes are suggested to play an essential role in the pathogenesis of pterygium, where they can serve as diagnosis markers or therapeutic targets.[75]

Despite numerous studies and different candidate genes, the genetic basis of pterygium remains to be elucidated and the mode of inheritance should be more deeply evaluated.

Viral etiologies

As part of a multistage pathophysiology, and next to UV radiation and inherited genetic factors, viral agents are regarded to have been involved in the development of pterygium. The role of these agents is another aspect of 'second hit' theory, where oncogenic viral infections stimulate the formation of pterygium in genetically susceptible individuals.[76] The probable role of human papilloma virus (HPV) and herpes simplex virus (HSV) in the pathogenesis of pterygium derives from a number of studies which reported the presence of these viruses in pterygium specimen.

The prevalence of HPV infection in pterygium has been reported to range from very low to 100%.[33,77,78] In a meta-analysis, an overall prevalence of 18.6% has been reported for HPV infection in pterygia.[79] The difference among studies in the prevalence of HPV in pterygium patients is attributable to various techniques used for virus detection, various geographic regions, and different life styles.[80] HPV type 16 and 18, which are considered as high-risk strains for cancer development, are the most frequent reported genotypes associated with pterygium.[77] The proposed mechanism of HPV-induced pterygium is the production of E6 and E7 factors by the virus, which affects the normal function of p-53.[78] In addition to the role of HPV in the pathogenesis of pterygium, the recurrence of pterygium after surgical removal is also suggested to be related to HPV.[32]

A similar disparity is obvious between studies that report the detection of herpes viruses in examined pterygium. Greek studies report the presence of HSV and cytomegalovirus in up to 45% of patients,[81,82] whereas a study conducted in Taiwan revealed a prevalence of only 5% for HSV detection in pterygia.[83] Another study from Turkey reported Epstein–Barr virus (EBV) DNA detection in 10% of the examined patients.[84]

Although there are uncertainties about the role of oncogenic viruses in the pathogenesis of pterygium, the current literature displays a disparity on the topic, which demonstrates the heterogeneous nature of pterygium pathophysiology. According to the current knowledge, it may be suggested that there is a possible role for viruses in pterygium development, at least in a subset of patients.

Clinical considerations and grading systems

The anatomy of pterygium can be divided into three parts: apex or head, neck, and body. The conjunctival portion with a base toward the medial canthus is known as the body. The invading portion which contains the apex of the tissue is called the head, and the communicating part between the body and the head, which overlies the limbus, is named the neck.[85] There may be a superficial corneal haze in front of the apex (cap or halo), even in early stages of pterygium growth.

Differential diagnoses of pterygium include corneal phlyctenule, elevated pinguecula, limbal dermoid, limbal squamous cell carcinoma (SCC) or ocular surface squamous neoplasia (OSSN), papilloma, and nodular scleritis. Among them, the most important diagnosis is OSSN.

The diagnosis of OSSN is usually made clinically, where feeder vessels, positive staining for rose bengal, and leukoplakic or papilliform appearance are evident. However, in real practice, neoplastic lesion sometimes lacks some symptoms, making it impossible to distinguish them from a benign ocular surface condition such as pterygium, pannus, or papilloma.[86] Histopathologic analysis remains the gold standard for the diagnosis of OSSN, and it is even more commonly recommended as recent reports have challenged the discrete borders of OSSN and pterygium. An optical cross-sectional biopsy through high-resolution optical coherence tomography (OCT) may also help clinicians to distinguish between benign and malignant conditions without performing excisional biopsy. In a study with the purpose of investigating the correlation between OCT findings and pathological evidences of OSSN and pterygium, it was reported that patients with suspicious limbal lesions who do not demonstrate a thickened epithelium in OCT scan can be managed without incisional biopsy.[87] As opposed to OSSN, images of pterygia revealed a normal thin epithelium with thickened subepithelial layer, and these features in OCT showed a sensitivity and specificity of 94% and 100% for differentiating pterygia from OSSN.[87]

Chronic and severe ocular surface inflammation or trauma, marginal corneal ulcer, or surgery may cause adhesions between conjunctiva and superficial cornea, which are known as pseudopterygium. As a distinguishing feature, it is believed that pseudopterygium is not attached to the underlying cornea throughout its full length, where a probe cannot be passed easily beneath the adhesive tissue (Bowman's probe test). It is notable that pseudopterygium is mainly an inflammatory process, while pterygium is considered as a degenerative response. In addition, pseudopterygium is a stationary condition, while true pterygium is a progressive ocular surface disease.

Tan and colleagues,[88] in a report in 1997, graded the pterygium based on tissue translucency. They believed that loss of translucency was correlated with the thickness of fibrovascular tissue, and this morphological characteristic may predict the rate of pterygium recurrence following surgical removal. They chose the visibility of episcleral vessels as the landmark of translucency. Accordingly, those pterygia with visible episcleral vessels beneath the body were graded as T1 or atrophic pterygia. In grade T3, all episcleral vessels are obscured by the opaque fibrovascular tissue of the pterygium body. Other pterygia which do not fall into these two grades are categorized as grade T2.[88]

Another grading system evaluates the effect of pterygium on corneal topography, which is determined by the extension of the head over the cornea.[89] Accordingly, grade 1 refers to the pterygium whose head is located between limbus and a point midway between limbus and pupil. Grade 2 indicates the pterygium with the head located between a point midway between limbus and pupillary margin and pupillary margin. In grade 3, the head crosses the pupil margin.[89]

The grading system proposed by Tan and colleagues[88] and Maheshwari[89] are clinically simple and useful classifications for primary pterygia. However, as the episcleral vessels are not visible in the majority of recurrent cases, a different grading system is required for recurrent pterygia. Accordingly, a grading system for recurrent pterygium was proposed with the purpose of predicting the success of surgical intervention.[90] Based on the external appearance, the recurrent pterygia were divided into four grades. Grade 1 consists of cases with a normal operative site. Grade 2 indicates the presence of fine episcleral vessels without fibrous tissue. Grade 3 represents cases with fibrous tissue not invading the cornea. Grade 4 indicates true recurrent pterygia with a fibrovascular tissue invading the cornea.[90]

In another study, the morphology of caruncle determines the grade of recurrent pterygia.[91] Both the flatness of the caruncle and its distance from the head of the recurrent pterygia are to represent a grading system. According to this grading system, the authors succeeded to predict the outcome of surgery for recurrent pterygia.[91]

Although most of the classifications are proposed to determine the surgical outcome of pterygium removal or the effect of the pterygium on the adjacent cornea, the first comprehensive grading system of primary pterygium for use in clinical research works was represented by Johnston and colleagues.[92] The main components of these grading systems include hyperemia, translucency, and the vascular network of the pterygium which are determined by images taken in the primary and lateral gaze. The hyperemia of both head and body of the pterygium is considered. In grade 0, no pterygium tissue presents. Grade 1 consists of

an indistinguishable translucent tissue with visible underlying episcleral vessels. The main feature of pterygium in this grade is dilated vessels, compared with the normal surrounding conjunctival vessels. Grade 2 pterygium indicates a pink tissue with increased density of vessels. The pterygium is translucent enough to allow the examiner to distinguish episcleral vessels. In moderate pterygium (grade 3), the pterygium is red in color, the vessels are engorged and tortuous, and the underlying episcleral vessels are indistinguishable. Grade 4 or severe pterygium is a deep and diffusely red tissue that completely obscures the underlying scleral tissue. The extension of the pterygium over the cornea is quantified by measuring the surface of the tissue encroaching onto the cornea in the primary gaze through standard slit photos and computer-assisted calculations. This grading system has been reported to possess an excellent intra- and intergrader reliability for the measurement of pterygium color and size.[92]

Pterygium complications

Corneal astigmatism

Although physical obscuration of the visual axis by pterygium is an absolute indication for surgical intervention, the visual function of the patient may be affected far earlier in the course of the disease, persuading the ophthalmologist to intervene before reaching the end stage. Pterygium can have a noteworthy impact on the corneal surface regularity indices through inducing astigmatism and surface asymmetry.[93,94] Pterygium usually results in a with-the-rule astigmatism due to the flattening of the horizontal meridian along its leading head.[95] The formation of a tear meniscus between the corneal center and the pterygium apex has been proposed for the underlying mechanism of horizontal corneal flattening.[96] The change of corneal curvature caused by pterygium cannot be evaluated by refraction or conventional keratometry because this change occurs over the nasal paracentral cornea in the horizontal meridian.[95] Therefore, computerized videokeratography seems to be the best tool in evaluating corneal topographic changes in pterygium patients.

It is now believed that topographical changes induced by pterygium are almost always reversible following pterygium removal.[97–99] However, pterygium-induced astigmatism should be evaluated through a reliable approach to predict the impact of pterygium removal on the visual function. Based on the preoperative refractive error, the residual postoperative astigmatism may be predicted through some proposed equations; however, ophthalmologists should always be cautious about using mathematical formulas in real-world clinical situations. The following equation is an example:

$$\text{Postoperative refractive cylinder} = 0.283 + 0.266 \times \text{preoperative refractive cylinder}.$$[89]

Larger pterygia are believed to induce higher refractive errors, and their removal is associated with more significant changes in corneal topography.[89,95,100–102] Lin and Stern reported that pterygium induces significant astigmatism when it exceeds beyond 45% of the corneal radius.[100] Tomidokoro and colleagues[95] suggested the percentage extension of pterygium on the cornea as a predicting factor for the degree of corneal irregularity. They proposed the following equation to express the relationship:

$$\text{Induced corneal changes by pterygium } (D) = 0.097 \times \text{pterygium extension} - 1.028.$$[95]

Similarly, Hochbaum and colleagues[103] postulated that the pterygium-associated corneal astigmatism can be calculated via a predictive model using horizontal extension of pterygium and resultant tractional force exerted onto the cornea. Oner and colleagues[104] reported that both the length and width of pterygium are responsible for pterygium-induced astigmatism. Mohammad-Salih[105] and colleagues demonstrated that pterygium can induce an astigmatism of more than 2 *D* when its total area is $\geqslant 6.2\ \text{mm}^2$. In a recent study, multivariate analysis revealed that two parameters, vascularity and horizontal length, influence the degree of astigmatism induced by the pterygium. Accordingly, to increase the reliability of the prediction model, the authors added vascularity index to the regression equation:[93]

$$\text{Pterygium-induced astigmatism} = 0.080 \times \text{RL}\ (\%) + 0.039 \times \text{VI} - 0.823,$$

where RL is the length of pterygium divided by the corneal horizontal diameter and VI stands for vascularity index which is determined through an anterior segment photograph using computerized algorithms.

The correlation between pterygium advancement and the increase in corneal irregularity was proved

in a recent study on 456 eyes. In this study, the Fourier harmonic analyses for a series of data revealed the precedence of topographical irregularity due to pterygium pregression.[94]

The effect of pterygium on the high-order aberrations of the cornea has also been described. Through the analysis of Placido disk data or anterior segment OCT outputs, it has been revealed that exacerbation of high-order aberrations due to pterygium progression alters with the size of the pterygium and diameter of the analysis.[106,107] In a recent study, it was shown that significant high-order aberrations were induced in 5.0-mm diameter when the head of the pterygium exceeded 25% of corneal diameter.[107] Initial findings assumed that the third-order aberration is mostly induced by the pterygium, while the contribution of the high-order aberration is relatively small.[108] It is currently believed that contributions of the coma and coma-like aberrations are the highest, followed by the spherical-like aberration. Such an association has not been observed in the spherical aberration.[107] Minami and colleagues showed that when the pterygium size was more than 45% and 40% of the corneal diameter, the coma-like and spherical-like aberration significantly increased, respectively. In contrast, there was no increase in the spherical aberration.[107] Anterior segment optical coherence tomography (AS-OCT) and Zernike analysis may facilitate objective grading of pterygium progression based on changes in corneal optics.[107]

Ocular surface squamous neoplasia

OSSN refers to a spectrum of ocular surface conditions ranging from mild dysplasia to invasive SCC.[109] There are same risk factors for OSSN and pterygium, so these two conditions can coexist or are even related. These common risk factors include UV radiation, chronic inflammation, chronic exposure to ocular surface irritants (such as dust), and oncogenic viruses (such as HPV).[16,110–112]

Two studies from Australia and three studies from North America have evaluated the coexistence of OSSN and pterygium in pathological studies of surgically removed pterygia. OSSN was present in nearly 10% of pterygium samples in Brisbane[112] and in 5% of cases in Sydney, Australia.[16] In the studies from North America, the prevalence of the coexistence of OSSN and pterygium has been reported to be less: around 2% in Montreal,[110] less than 2% in Florida,[113] and 0% in Toronto.[114] This discrepancy observed in studies is attributable to variations in UV exposure across geographic regions. It is possible that pterygia diagnosed in regions with high UV exposure are more susceptible to carry neoplastic features. Another factor that confounds the prevalence of atypia associates with pterygium is the criterion used for surgical removal by different studies.

Older age and inferiorly located pterygia are two factors reported to be associated with higher prevalence of OSSN in pterygium samples.[113] On the contrary, Kao and colleagues[115] reported no significant difference in the average age of patients with pterygium associated with OSSN and patients having pterygium without OSSN. They concluded that age is not a significant risk factor for the development of OSSN in pterygium cases.

Hirst and colleagues[112] reported no case of recurrence after pterygium removal in their samples of simultaneous OSSN and pterygium, while a recurrence rate of 11% at 1 year was reported for the pterygia associated with OSSN in the Florida study. It is as same as the recurrence rate reported for OSSN not associated with pterygium, which is around 12%.[116] Most OSSN cases in the Florida and Montreal studies were found to have corneal intraepithelial neoplasia (CIN) I, while CIN II was the most frequent neoplasia in the Australian cases. It may also be justified in part by the higher UV exposure in Australia, which may cause a rapid lesion progression.

According to the data presented above, it is advisable to send all pterygium specimens for pathological studies following surgical removal. In cases with coincident OSSN, close follow-up for screening of recurrence or new lesions is recommended.

Surgical management of pterygium

Indications of intervention

As the excised pterygium will cause a corneal scar, earlier excision of a progressive pterygium before involving the central cornea will save the visual axis from obscuration by a permanent corneal opacity. A progression reported by the patient may be inferior to a documented growth by the surgeon, which is possible through recording the size of the pterygium during follow-up examinations.[117] Similarly, limited eye movement secondary to a large pterygium is an apparent indication

for surgical intervention. The presence of atypical features resembling dysplasia is another indication for an early intervention, as delayed excision of a suspicious neoplastic lesion will predispose the patient to intraocular or systemic involvement. Beyond these definite indications, there are some other conditions which may arise controversy among ophthalmologists. Pterygium may be responsible for a vision-impairing astigmatism even before reaching to the corneal center, and it may persuade the surgeon for an early surgery with the purpose of correcting the patient's refractive error. However, according to the current literature, it is difficult to predict the amount of astigmatism reversion following the surgery. The benefit of probable reduction in corneal astigmatism should be weighed against the cost and complications of the surgery, especially the rate of pterygium recurrence. Pterygium removal for the control of chronic signs and symptoms, including redness and irritation, is still open to debate; other coincidental ocular surface conditions rather than pterygium, including blepharitis and dry eye, should always be considered by the surgeon as the etiology of the presenting symptoms. There is roughly the same situation for pterygium removal as a cosmetic intervention. In these circumstances, it is important to consult the patient about the procedure, the recovery period following the surgery, and the rate of pterygium recurrence.[117]

Surgical outcome

The major end point in pterygium surgery remains to be the recurrence rate. It is normally defined as a corneal recurrence of fibrovascular tissue and has been widely used in scientific articles for a comparison between different methods of pterygium removal. Pterygium recurrence should be distinguished from common postoperative corneal opacity and scar which is left following adequate removal of the tissue. The most important step in the management of pterygium seems to be the modification of recurrence risk using clinical information and selecting suitable surgical methods.

Although many studies have focused on the role of surgical techniques and surgery-related factors in the recurrence rate, there are other preoperative features that may predict the probability of pterygium recurrence, independent of the type of the surgery. Younger age has been reported to be associated with a higher rate of pterygium recurrence.[118] Ha and colleagues[118] believed that younger age is a risk factor for the recurrence of pterygium following excision and graft surgery, and it may be linked to rapid re-epithelialization, aggressive angiogenesis, and prompt collagen synthesis in young patients. Aidenloo and colleagues,[119] in an observational study conducted on 310 patients, reported that younger age, larger tissue, and recurrent pterygia were associated with a higher rate of recurrence following limbal-conjunctival autografting. In a retrospective study of 205 eyes, the size of the pterygium was reported to be the only preoperative feature related to the recurrence rate following current surgical technique, particularly autografting.[120] In another study, ethnicity was revealed to be related to the recurrence rate, where Hispanic and dark-skinned patients experienced a higher rate of pterygium recurrence following excision and limbal autologous grafting.[121] Tan and colleagues[88] postulated that the flesh-like morphology of pterygium was correlated with a higher recurrence rate, when the pterygia were excised with bare sclera or autografting techniques. Other patient-related characteristics proposed to be associated with higher recurrence are active preoperative growth of the pterygium, preoperative disfiguration of the caruncle, coincidental ocular surface disease, and genetic predisposition.[122]

The surgery-related factors, however, are the main modifiable options for lowering postsurgical recurrence of pterygium.[122] These factors have been studied in three major fields: optimization of the pterygium tissue removal, modification of basic surgical methods for repairing the surgery site, and using preoperative, intraoperative, and postoperative adjuvant therapies.

The crucial features of an optimal pterygium surgery include appropriate removal of proliferative epithelial cells, thorough removal of subconjunctival fibrovascular tissue, and adequate covering of the surgery site.[122] Pterygium cells should be removed as they altered LSCs which are supposed to be the initiators of pterygium development through their proliferative features. Pterygium fibroblasts are also involved in the recurrence and are the main target of adjunctive therapies proposed for pterygium surgery, such as mitomycin C (MMC) and 5-fluorouracil (5-FU). Finally, an appropriate cover for the underlying bare sclera will reduce severe postoperative pain and facilitate re-epithelialization. Severe postoperative inflammation may be responsible for an exaggerated repair response in the site of surgery and subsequent regrowth of the pterygium.[123]

The bare sclera technique was the first surgical technique in which the pterygium conjunctiva and subepithelial scar and Tenon are removed, leaving bare sclera exposed.[124] This technique is associated with high rates of pterygium recurrence and postoperative complications such as scleral necrosis and infection. Modifications to the bare sclera technique have included simple conjunctival closure, conjunctival or limbal autograft, and amniotic membrane transplantation (AMT). Adjuvant options, such as beta irradiation, mitomycin, 5-FU, anti-VEGF agents, and cyclosporine A (CsA), have been added to these surgical methods to reduce the recurrence of pterygium (Table 1).

Topical antibiotics, topical steroids, and analgesics are routinely used with different protocols in the immediate postoperative period. Although the selected protocol is commonly dependent on the surgeon preference and the patient condition, there are some recent studies with the purpose of comparing these protocols, respective to the patient compliance and complication rate. For example, a recent study of 120 pterygium surgeries reported that 4 months of topical steroids in a tapering fashion following pterygium removal shows more compliance rate and less complication, in comparison with a protocol of topical steroids tapered over 5 weeks.[125]

Basic surgical technique and adjuvant options

The isolated bare sclera technique is the quickest surgical approach to pterygium removal, requiring the least tissue manipulation. However, it is abandoned for a high postoperative recurrence rate. Some reports have estimated a recurrence rate of nearly 90% following bare sclera technique.[126] A meta-analysis of randomized clinical trials concluded that the risk of pterygium recurrence for bare sclera technique was up to 25 times higher, compared with the conjunctival autograft technique.[127]

To reduce the recurrence risk, beta radiation with strontium-90, and triethylene thiophosphoramide (thiotepa) and 5-FU were used as adjuvant treatments for the bare sclera technique.[128–132] Most of these adjuvant options have been abandoned due to the presence of safer and more effective alternatives.

Intraoperative or postoperative MMC is another adjuvant option which has been studied widely during recent decades. A reduction in pterygium recurrence has been reported following the administration of both 0.02% and 0.04% MMC, and the most common duration of treatment has been 3–5 min. In a study, the bare sclera approach with MMC 0.02% applied for 5 min decreased recurrence rates from 45% to 5%, and no complication was reported.[133] Several randomized trials on primary pterygium have concluded that intraoperative application of MMC with different concentrations (0.002–0.04%) and application times (3–5 min) significantly reduced the recurrence rate, compared with bare sclera excision.[134–136]

Postoperative MMC has also been used with different concentrations and dosage protocols, where all the studies have reported a significant reduction in recurrence rate, compared with the isolated bare sclera technique.[50,137] In two trials, 0.02% MMC was used twice a day for 5 days following the surgery.[50,137] Higher concentrations were used in other trials, where 0.04% MMC was administered 4 times a day for 1 or 2 weeks postoperatively.[137,138] According to these trials, the recurrence rate of pterygium following combined bare sclera and postoperative MMC ranges from 3% to 38%.[126] Some studies compared results between intraoperative and postoperative application of MMC and reported no significant differences in recurrence rate for either primary or recurrent pterygium.[139–142]

In addition, there are studies that have evaluated the efficacy of preoperative subconjunctival injection of MMC as adjunctive therapy for pterygium surgery. In a prospective study of 36 patients, 0.1 ml of 0.15 mg/ml MMC was injected subconjunctivally into the head of the pterygium 1 month before bare sclera surgical excision.[143] A recurrence rate of 6% was observed after 2 years, and no wound-healing complication was reported. In a randomized comparative study, 50 eyes with recurrent pterygium were randomly divided into the preoperative MMC injection group and the postoperative topical MMC group. In the first group, 0.1 ml of 0.15 mg/ml of MMC was injected a day before bare sclera pterygium excision surgery. The difference between the recurrence rates and the complications was statistically insignificant, and the authors concluded that preoperative subconjunctival injection of low-dose MMC is an effective modality for the management of recurrent pterygium.[144]

Many randomized controlled trials (RCTs) have recently been performed to assess the efficacy of

Table 1. Summary of surgical techniques and adjuvant options for the treatment of pterygium.

The basic surgical technique	Adjuvant option	Recurrence rate according to prospective comparative or noncomparative studies (%)
Bare sclera	None	24–89
	Beta irradiation	0.5–52
	Topical postoperative thiotepa	3–45
	Intraoperative 5-FU	11–36
	Preoperative MMC injection	4–6
	Intraoperative MMC application	3–38
	Postoperative topical MMC	0–38
	Intraoperative subconjunctival bevacizumab injection	57.6
	Postoperative topical bevacizumab	0–41.7
	Postoperative topical cyclosporine 0.05%	12–22.2
Conjunctival or conjunctiva-limbal autografting	None	1–40
	Intraoperative 5-FU	3.7–12
	Intraoperative MMC	0–9
	Postoperative topical MMC	6.5–21
	Subconjunctival bevacizumab injection	0–18.8
	Postoperative topical cyclosporine 0.05%	3.4–7.5
Amniotic membrane transplantation	None	2.6–42.3
	Intraoperative MMC	16–21

FU, fluorouracil; MMC, mitomycin C.

anti-VEGF agents, combined with basic pterygium removal techniques, in reducing the postoperative recurrence rate. Four trials had evaluated the efficacy of adjuvant topical or subconjunctival bevacizumab, and compared the recurrence rate with the isolated bare sclera technique. Shenasi and colleagues[145] evaluated the effect of subconjunctival bevacizumab immediately after the excision of primary pterygium and concluded that the combination therapy is well tolerated, but it cannot significantly reduce the recurrence of pterygium. Kasetsuwan and colleagues[146] assessed the efficacy of topical bevacizumab 0.05% after the excision of primary pterygia of 22 patients. The recurrence was found in 33.3% and 90.00% of patients in the bevacizumab and placebo groups, respectively, with no significant adverse events. Hwang and Choi[147] compared the recurrence rates of pterygium removal surgery associated with topical MMC, cyclosporine, and bevacizumab. They observed no difference between the control group and the group that received topical 2.5% bevacizumab following the bare sclera surgery. In a recent study, two different concentrations of topical bevacizumab (5 *versus* 10 mg/ml) were used following pterygium removal of 90 patients,

and the recurrence rates were compared between the groups. Pterygia recurred in 13.3% in the 5 mg/ml group, while no recurrence was observed in the 10 mg/ml group. Thus, the authors concluded that 10 mg/ml concentration of topical bevacizumab is more effective than 5 mg/ml dose in preventing pterygium recurrence.[148]

Postoperative topical CsA is another adjuvant treatment used to reduce the recurrence rate of pterygium after surgical removal.[149] In a comparative study of 31 patients who had undergone bilateral pterygium removal using the bare sclera technique, the pterygium recurred in 12.9% of eyes treated postoperatively with CsA 0.05%, while the recurrence rate was 45.2% in the control group. The control group had a 7.37 times higher risk of recurrence of pterygium compared with the treatment group.[149] In another study, it was concluded that pterygium removal surgery combined with topical 0.5 g/l CsA was efficient for the prevention of pterygium recurrence.[150] In the study by Hwang and Choi,[147] 20.6% of the eyes in the cyclosporine group showed recurrence, which was lower than that in the control group. In a randomized controlled study enrolling 36 eyes that received bare sclera pterygium excision, Turan-Vural and colleagues[151] investigated the effectiveness of postoperative 0.05% CsA (4 times a day for 6 months) in the prevention of pterygium recurrence. They reported that recurrence occurred in 22.2% of the eyes in the treatment group, which was as low as half of the recurrence rate in the control group.

Conjunctival or conjunctiva-limbal autografting

Described by Kenyon and colleagues[152] in 1985, conjunctival autografting consists of covering the scleral bed with a free graft harvested from adjacent conjunctiva after pterygium removal. Although conjunctival autografting technique requires more operative time and expertise, the procedure is associated with lower recurrence rates, compared with the bare sclera technique alone. The graft can be fixated to the adjacent tissue by sutures or adhesive products; the main complications of the procedure remain to be postoperative ocular discomfort and irritation, and rarely displacement or retraction of the graft. The Tenon's tissue associated with the graft may serve as a new reservoir for further proliferation of the fibroblasts and pterygium recurrence. It is important to have a Tenon-free graft to avoid the recurrence rate, as it has been established in recent studies.[153]

Several trials have demonstrated the superiority of conjunctival autograft technique over the bare sclera method in the reduction of postoperative recurrence in primary and recurrent pterygia.[50,153–155] Furthermore, the conjunctival autografting technique is as effective as the combined bare sclera technique and MMC in reducing the recurrence rate.[156–159] However, other studies reported a lower recurrence rate after conjunctival autografting, compared with combined bare sclera and MMC.[160] The reported rates of pterygium recurrence following conjunctival autografting range from 1% to approximately 40%.[126] For primary pterygium, many studies have reported recurrence rates of lower than 15%, while for recurrent pterygia it lies within a range of 30–33%.[161–165] When combined with adjuvant options, recurrence of pterygium 3 months after conjunctival autografting ranges from 0% to 16.7%, while the recurrence at 6 months after the surgery ranges from 3.33% to 16.7%.[166]

The recurrence rate after autografting technique can be lower when the surgery is combined with intraoperative or postoperative MMC therapy.[167,168] The recurrence rate after combined intraoperative MMC and conjunctival autograft technique varies from 6.7% to 22.5%.[169–172] No statistically significant difference has been reported between intraoperative and postoperative application of MMC in conjunctival graft surgery, although the recurrence rate following intraoperative application of MMC was lower (0–16% *versus* 6–22.5%, respectively).[126]

Fibrin glue is an alternative for graft suturing in pterygium surgery.[173] Shorter operation time and lower recurrence rate are advantages of fibrin glue in pterygium surgery; higher cost, risk of transmitted infections, and higher risk of dehiscence and graft retraction, however, have limited its usage. Koranyi and colleagues[174] reported a 5.3% recurrence rate when fibrin glue was used, while suture-assisted technique resulted in a recurrence rate of 13.5%. In situ blood coagulum technique has also been proposed to reduce the risk of infection transmission and hypersensitivity reactions associated with fibrin products. Fibrin glue–assisted conjunctival autografting has been comparable with in situ coagulum with respect to the recurrence rate; however, the latter has been associated

with higher risk of graft displacement.[175,176] Kumar and Singh conducted a trial on 60 pterygium cases and compared the three methods of conjunctival graft fixation: fibrin glue, suturing, and autologous blood. They reported that fibrin glue is the most efficient technique for conjunctival graft fixation in pterygium surgery with the least operation time, ocular discomfort, and recurrent rate.[177]

Amniotic membrane transplantation

Amniotic membrane (AM) can be beneficial during surgical reconstruction of excided pterygium site through a number of mechanisms. Stromal component and overlying basal lamina of AM resemble the architecture of normal human conjunctiva, where it can provide a platform for the growth of conjunctival and corneal epithelial layer. The covering feature of AM reduces postoperative pain through protecting scleral nerve ends and reduces evaporation. As a theory, the presence of AM may provide a barrier for abnormal growth of conjunctival stem cells in the underlying limbus, facilitating the proliferation of normal LSCs.[178]

There are several trials examining pterygium recurrence rates after using AM graft, compared with conjunctival or limbal autograft. Four studies demonstrated a higher pterygium recurrence rate in the AMT group.[155,157,179] A meta-analysis of 20 studies in 2016 revealed that AMT is associated with a higher risk of recurrence 6 months after surgery, compared with conjunctival autografting, and the inferiority of AMT is present in both primary and recurrent pterygia.[166] According to the current literature, recurrence of pterygium 3 and 6 months following surgery with AMT ranges from 4.76% to 26.9% and 2.6% to 42.3%, respectively.[166]

Intraoperative MMC is an adjuvant option proposed for reducing pterygium recurrence following AMT technique, while a trial reported no difference in recurrence rates when AM was used alone or in combination with MMC 0.025% that was applied intraoperatively for 3 min.[180] In other studies, the recurrence rate of pterygium following combined AMT technique and intraoperative MMC ranges from 16% to 21%, which shows no prominent difference, in comparison with AMT alone.[126,180] In a recent study, however, conjunctiva-limbal autograft technique with intraoperative 0.02% MMC was as effective in treating recurrent pterygium as AMT with MMC.[181]

Complications of pterygium surgery

Intraoperative hyperemia and hemorrhage of the conjunctiva is a common event. Controlling the hemorrhage through thermal cautery or pressure hemostasis reduces the surgery time and facilitates the surgical technique. Recently, it has been recommended applying brimonidine tartrate before the surgery to improve the safety and comfort of the surgical area by brimonidine-related conjunctival whitening.[182]

Postoperative complications in pterygium removal can be related to the surgical technique itself or to any of the adjuvant options used. Most of the immediate postoperative complications of pterygium surgery are not vision-threatening and resolve rapidly. These complications include graft edema, hemorrhage or hematoma under the graft, and corneal scarring. Pressure bandages and topical anti-inflammatory treatment can accelerate the resolution of these conditions. Rarely, deep and severe corneal scars may require lamellar keratoplasty. Corneal epithelial defects and early postoperative chemosis noted in initial postoperative examination are usually healed within 24 h.[129]

Scleral thinning or ulceration is a vision-threatening complication that is related to the use of intraoperative beta irradiation or intraoperative and postoperative MMC, whether AMT or autologous graft is employed to cover the bare sclera or not. A similar range of scleral thinning rate has been reported for both intraoperative and postoperative MMC with both 0.02% and 0.04% concentrations.[126] Some studies have reported a relationship between higher scleral thinning rate and increasing MMC concentration and duration of application.[136,183] Delayed epithelialization is another serious complication of MMC in pterygium surgery. Similar to scleral thinning, delayed epithelialization may occur in both intraoperative and postoperative MMC.[50,136,141] Iritis has also been reported following intraoperative and postoperative MMC use.[134,140,142]

The safety and tolerability of both bevacizumab and CsA as adjuvant options in pterygium surgery have been emphasized in several studies. In a meta-analysis of 18 RCTs, it was reported that postoperative complications of pterygium surgery

were not significantly different between adjuvant bevacizumab group and control group.[184] In another meta-analysis of trials using CsA as adjuvant for pterygium surgery, results showed that the adjuvant use of CsA seemed to increase the safety of surgery respective to all complications and conjunctival granuloma, while in the case of scleral thinning there was no difference between the CsA group and the control group. Thus, CsA and bevacizumab administration can be regarded safe adjuncts to pterygium treatment.[185] Postoperative administration of topical bevacizumab can elevate the risk of corneal epithelial defects.

Conclusion

The main risk factor for the development and progression of pterygium remains to be UV exposure. The role of viral agents and the heredity have been suggested, but the literature lacks reliable conclusions. In addition, these hypotheses have neither changed the practice, nor presented additional prophylactic and treatment options. Pterygium should be considered as a diffuse ocular surface disease, and concomitant conditions such as dry eye should be addressed. The cells responsible for the development of the pterygium are altered limbal stem cells, and stromal changes are involved in the progression of the disease. As the altered stem cells are mainly located in the head of the pterygium, complete removal of the apex is critical in the surgical excision of the pterygium. The clinical examination of a patient with pterygium should be given more importance than the past, as atypical features and secondary corneal irregularities may justify earlier surgical intervention. Association of pterygium with ocular surface neoplasia has been reported in several studies. Pterygium may induce both astigmatism and high-order aberrations of the cornea, where the amount of both are correlated with the size of the pterygium. Surgical removal of the pterygium can reduce the corneal irregularities, giving a refractive value to an earlier surgical intervention. Also, a pretreatment classification based on the size, texture, and vascularity of the pterygium may provide a prediction for the postoperative recurrence rate. It is recommended that excised pterygia, particularly in atypical cases, be sent for histopathologic studies. The procedure most advised for the repair of the surgical site is conjunctival and conjunctiva-limbal autografting, and the use of adjuvant intraoperative MMC seems to be more effective than other adjuvant options to reduce the risk of postoperative recurrence. The application of CsA and bevacizumab in the site of excised pterygium has been reported to be safe; however, reports on the efficacy of these adjuvant treatments are still inconclusive.

Author contributions

A.A. and T.S. performed and analyzed the literature and contributed to the writing of the manuscript. S.F. edited and revised the manuscript.

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