UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
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UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Masters of Medicine in Ophthalmology

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Study number: UFS-HSD 2019/0464/2506

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Date of Submission: 9 December 2019

THE PREVALENCE OF PTERYGIUM RECURRENCES AND ASSOCIATED RISK FACTORS AT THE UNIVERSITAS ACADEMIC HOSPITAL COMPLEX IN BLOEMFONTEIN

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Submitted in fulfilment of the requirements in respect of the Master's Degree MMed in the Department of Ophthalmology in the Faculty of Heath Science at the University of the Free State

Submission date: 9 December 2019

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Declaration

I, Christian Engelbrecht, declare that the coursework Master's Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree qualification for Masters of Medicine in Ophthalmology at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education.

Acknowledgement

I would like to acknowledge and express my gratitude to my supervisor Professor WJ Marais, the HSREC of the University of the Free State, the Department of Health and the Department of Ophthalmology at the University of the Free State.

Dedications

This study has been dedicated to the patients who seek treatment at the Department of Ophthalmology at the University of the Free State, for your contribution to our ever expanding understanding of pathology and eye care.

Abstract

Aim: To find the prevalence of and associated risk factors of pterygium recurrences in patients who underwent pterygium surgery at the Universitas Academic Hospital Complex.

Methods: A retrospective cross sectional study of all the patients who underwent pterygium surgery at the Universitas Academic Hospital Complex between January 2016 and December 2018. All patients who received their primary surgery at the Universitas Academic Hospital Complex were included.

Results: A total of 117 eyes from 94 patients who underwent pterygium surgery were identified. The proportion of females was 80% (n=94). Ages ranged from 20 to 75 years with a median age of 49 years. Most patients (83%) presented 6 months after noticing symptoms related to the pterygium. These symptoms included: redness (30%), tearing (13%) and foreign body sensation (10%). Inflammation was noted in 21% of patients. The most common surgical procedure performed on these patients was a conjunctival autograft (74%), followed by a conjunctival rotational flap (10%), amnion graft (10%) and bare sclera (2,5%).

The bare sclera technique was used in a total of 3 cases, 2 of these cases (66,7%) had a recurrence. A conjunctival autograft was used in 86 cases, of these 10 cases (11,6%) had a recurrence. In a total of 17 cases where a conjunctival rotation flap was used, 3 patients (17%) had a recurrence. An amnion graft was used in 12 patients, 6 of them (50%) had a recurrence. The total recurrence rate was 21 (18%).

Conclusion: Postoperative recurrences are a common complication of pterygium surgery. Compared to the bare sclera technique and amnion grafts, conjunctival autografts and conjunctival rotational flaps had lower recurrence rates.

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Abbreviations

Anti-VEGF: anti-vascular endothelial growth factor

MMC: mitomycin C

TGF-beta: transforming growth factor beta

UV: ultraviolet

5-FU: 5-fluorouracil

Chapter 1

1. Literature review

1.1 Introduction

A pterygium is a degenerative condition of the eye. It is a wedge shaped growth consisting of fibrovascular tissue. It was described by the first recorded ophthalmic surgeon, Susruta, as early as 1000 BC.[1] It is continuous with the bulbar conjunctiva. The growth extends a variable distance onto the cornea. It usually presents bilaterally, on the nasal aspect of the eye. It is most commonly found in the dry equatorial regions. There is an association with exposure to environmental factors including dust, wind and ultraviolet (UV) light.[2]

1.2 Prevalence

There is a worldwide occurrence of pterygia, with a high prevalence around the “pterygium belt”. This is the area between 30 degrees north and 30 degrees south of the equator. The prevalence varies widely from 0,3% to 29% depending on the latitude. Increase in geographical latitude is related to a decrease in the prevalence of pterygium.[3]

In a meta-analysis involving 20 studies, spanning 12 countries, the pooled prevalence rate was estimated at 10.2%.[4] In countries lying within the “pterygium belt” a prevalence of up to 22% has been shown. When compared to countries outside this zone a smaller prevalence is noted. Only 2% of the general population in these areas are affected. In these low prevalence areas, the affected patients usually report increased levels of UV exposure either due to outdoor working conditions or recreational activities.[5] The prevalence was also higher in the rural population when compared to urban. This can be explained by an increased involvement in outdoor work.[4] UV exposure has also been linked to other ophthalmological pathology. This includes cataract formation, spheroidal degeneration and ocular surface squamous neoplasia.[6]

1.3 Histology

The histological characteristics of a pterygium show a basophilic degeneration of the subepithelial substantia propria and stromal collagen fragmentation. This is also known as elastotic degeneration. Mild squamous metaplasia may be seen in the overlying epithelium. This is represented by a loss of goblet cells and keratinization of the surface.[7] A pinguecula is similar to a pterygium in its location and origin. A pinguecula is a thickening of the bulbar conjunctiva, with the same histological characteristics as a pterygium. The distinguishing feature between the two is that a pterygium extends onto the cornea and has an absence of the Bowman's membrane. A rupture in Bowman's membrane results in a firm attachment of the pterygium to the underlying stroma. Pterygia present with an increase in mast cells.[8]

1.4 Pathogenesis

The pathogenesis of this disease is not yet fully understood, however certain risk factors have been identified. These risk factors are discussed below

Inheritance has been shown in a small portion of cases.[9] There are early reports of an autosomal dominant inheritance pattern. However, the independent trait could not be identified and these family members shared an increase in environmental risk factors.[5] There is a difference in the prevalence of pterygia among different races and ethnicities living in the same geographic location. This suggests an inherent link between pterygia and race.[10]

Environmental factors that have been associated with the pathogenesis of pterygia are wind, heat and sunlight exposure in the form of ultraviolet (UV) light. Pterygia appear to be more common in outdoor workers compared to indoor workers.[11] One of the main risk factors is UV radiation exposure. The evidence suggests that there is no particular period of life where exposure has a greater influence than other periods. This implies that prevention and ocular protection is important in all ages.[4,11,12] A slight male predominance can be attributed to the fact that in many countries males usually spend more time working outdoors. Ocular surface changes have also been associated with the formation of pterygia. There is an association with dry eyes and a decreased tear break up time.[5] Environmental factors are implicated in the formation of a nasal or temporal lesion. If a pterygium-like lesion

develops on any other axis, other than nasal or temporal, it is highly suggestive of a pseudo-pterygium. A pseudo-pterygium is usually secondary to trauma or inflammatory conjunctival conditions and is not a true pterygium.[13]

The epithelial cells in a pterygium have an abnormal expression of Ki-67, as well as dysregulation of tumour suppressor genes. These tumour suppressor genes include p53 and p63. Due to dysfunction of these tumour suppressor genes, cases of pterygia and pinguecula have the potential for malignant transformation. However, this transformation is rarely seen.[7] A mutation in the tumour suppressor gene p53 is implicated in the pathogenesis of pterygia. This mutation has been shown within the limbal epithelial cells and is most likely caused by UV irradiation.[8]

Viral infections have been implicated in the cause of pterygia. These include human papilloma virus, herpes simplex virus and cytomegalovirus. A possible pathogenic model is suggested in which these oncogenic viruses together with genetic predisposition and environmental factors participate in a multi-step process, all contributing to the pathogenesis of a pterygium.[13]

Other pathogenic factors include the following:

- Inflammatory mechanisms
- Neo-angiogenic upregulation.[14]

1.5 Clinical Presentation

Pterygia are found in the palpebral fissure, growing from the conjunctiva onto the cornea. Pterygia grow towards the visual axis and can induce significant astigmatism and abnormalities of the tear film. This can cause blurred vision. When inflamed, pterygia can cause ocular irritation, foreign bogy sensation and tearing. Patients may have complaints regarding the cosmetic appearance. Restrictive strabismus due to subconjunctival fibrosis and symblepharon formation has been described in severe or recurrent cases.[6] In severe cases the pterygium can involve the visual axis and grow over the entire corneal surface. These cases can present with severe vision loss.[15]

A pterygium is made up by three different segments, namely, a cap, head and body. The cap is an avascular zone on the leading edge of the pterygium. There is usually a variation in the history of growth of a pterygium. Sometimes characterized by extended periods of decreased growth activity. During these extended periods of inactivity, Stocker lines may form. These are linear iron deposition in the corneal epithelium caused by tear film lactoferin.[5] Islets of Vogt are elevated white opacities consisting of abnormal epithelial cells. Stocker lines and Islets of Vogt are usually seen at the leading edge of a pterygium.[16] Corneal clouding can be seen in severe cases and can be associated with the formation of a corneal or scleral dellen.[5]

1.6 Treatment

Conservative medical treatment can be used for mild slow growing cases of pterygia. Topical lubrication can be prescribed for mild irritation. A short course of topical steroids can be used if there is mild inflammation. Patients should be counselled on preventative measures like sunglasses and hats to reduce UV radiation exposure.[6]

Surgery is the management of choice for a symptomatic pterygium. Chronic ocular irritation and decreased vision are included amongst the main indications for surgery.[17] Careful dissection of the pterygium head and diligent excision of the involved stroma should be carried out to ensure a promising postoperative outcome. Surgical removal of the subconjunctival fibro-vascular tissue ensures excision of active fibroblasts. This decreases the risk of recurrence.[18]

Covering of the bare sclera after excision on the pterygium promotes epithelial growth over the defect. There are different techniques used to close the scleral defect, these include the use of a conjunctival autograft, a conjunctival rotation flap or an amnion membrane graft. Leaving the bare scleral defect exposed after excision is associated with pain and hypertrophy of the wound and the surrounding conjunctiva. This increases the risk of recurrence.[19]

Control of postoperative pain can be achieved by the use of bandage patches and bandage contact lenses. The use of anti-inflammatory agents and artificial lubricants are also indicated in pain control and corneal healing. Autologous serum eye drops

can be used for rapid epithelial healing. Several intraoperative and postoperative adjunct treatments are available to decrease postoperative fibroblast activity.[14]

The main complication of pterygium surgery is recurrence. This is characterized as the development of a fibro-vascular growth at the excision site. When these fibro-vascular growths recur, they may be of a greater extent than the primary pterygium.[5] There is a 50% chance that the pterygium recurrence will occur within the first 120 days following excision surgery. In 97% of cases the recurrence occurred within 12 months of the excision.[10]

Unfortunately, there is no single standardized surgical method currently recommended. Variations in the rate of pterygium recurrence can be attributed to the size of surgical excision, the age of the patient, the surgical experience of the surgeon and variations in surgical technique.[20]

The methods of surgery that are widely used will be discussed below.

i) Bare sclera

Early pterygium surgery included detachment and surgical excision of the pterygium head from the cornea. This was then modified into the bare sclera technique.[5] During the bare sclera technique, the lesion is removed from the cornea together with the peri-limbal conjunctiva. The remaining rim of conjunctiva is then sutured into the sclera to create a barrier preventing remnant pathological tissue from re-growing towards the cornea. The remaining sclera is left bare, to re-epithelialize from the surrounding conjunctival rim. This technique carries a high recurrence rate (24%-89%).[21,22] The bare sclera technique is simple to perform and is associated with a short surgical time.[14] Due to the high recurrence rate, other techniques have been developed to cover the scleral defect and install a barrier of normal conjunctiva to prevent regrowth.[5]

ii) Conjunctival autograft

This technique requires harvesting a free conjunctival graft from the same or other eye of the patient. The graft is usually harvested from the para-limbal region.[6] This has the added advantage of providing normal stem cells to the limbal area where the

pterygium has been excised.[5] Accurate measurement of the defect created by excision of the pterygium and the graft tissue can lower the rate of recurrence. A graft size that is slightly larger than the exposed sclera should be used.[23] The graft size can be measured with a caliper and marked by a marker. Normal saline or local anaesthetic can then be injected subconjunctivally to separate the graft from the Tenon's layer. It is vital to remove the Tenon's capsule from the harvested graft.[3] The graft should be handled carefully to prevent damage. Graft reversal should also be prevented while moving it into place. This graft is then secured to the exposed scleral bed in the area of the excised pterygium with either sutures or fibrin glue. The use of sutures to secure the conjunctival graft is associated with an increased surgery time.[24] Sutures are also associated with a number of complications. These complications include postoperative discomfort, inflammation, infection and suture granuloma formation. The use of fibrin glue can provide an alternative. Complications related to the use of fibrin glue include graft dislocation. Autologous blood serum can be used as an alternative to fibrin glue. The recurrence rates for the conjunctival autograft technique varies between 3,3% and 13,5% for the primary procedure and up to 33,3% in cases of recurrent pterygium surgery.[14] Autografts are usually harvested from the superior temporal conjunctiva.[6] This can cause iatrogenic damage to the conjunctiva in that region. Up to 37% of patients can develop some form of scarring at the donor sight. This may have an influence on future glaucoma surgery.[20]

A conjunctival rotation flap can also be used. This is a relatively simple procedure with a shorter surgical time when compared to the free autograft.[25] The conjunctival rotation flap involves the mobilization of a conjunctival flap from the superior or inferior conjunctiva. This flap is then sutured to the defect created during the pterygium excision, thus creating a barrier of normal conjunctiva to block the recurrence of the pterygium.[5]

iii) Amnion graft

The amnion membrane consists of the inner layer of the placental membrane. It is made up of a basement membrane and an avascular stromal matrix. During surgery the amnion membrane is attached over the area of bare sclera with the basement

membrane facing upwards. Sutures or fibrin glue can be used to secure the amnion graft.[14]

Ocular surface inflammation plays a significant role in the recurrence of pterygia.[26] The effectiveness of amnion membrane grafts in pterygium surgery is due to the inhibition of pathological neovascularization, promotion of conjunctival epithelialization and the prevention of inflammation. It is effective in suppressing transforming growth factor beta (TGF-beta) signaling and the transformation of myofibroblasts in pterygia. The recurrence after amnion membrane grafting varies between 3,8% to 40,9%.[20]

Advantages of using amnion grafts to cover the exposed sclera include shorter operating times and preserving the conjunctiva for future glaucoma filtering procedures.[27] Amniotic membranes are useful for covering extensive surgical defects in cases of large or combined medial and lateral pterygium removal.[14] When comparing amnion membrane grafts to conjunctival autograft, a lower recurrence rate is shown with the conjunctival autograft.[21,22]

iv) Adjuvant treatments

Adjuvant treatment can be combined with all the above mentioned surgical techniques. Commonly used adjuvants are discussed below.

Mitomycin C (MMC) is an alkylating agent, isolated from the fungus Streptomyces Caepitosus. It inhibits mitosis, protein and DNA synthesis by DNA cross linking. It also inhibits fibroblast proliferation. It can be used intra and postoperatively. No standardized treatment protocol is currently available.[28]

Four randomized control trials examining primary pterygia noted that MMC used in concentrations varying from 0.02% to 0.04%, applied intraoperatively for a time period of less than 2 minutes, significantly reduced the recurrence rate of pterygia. MMC can also be given postoperatively as eye drops.[5] No substantial differences were noted between the use of intraoperative scleral application of MMC and

postoperative MMC at a concentration of 0.02% for 5 days when used in patients undergoing a rotational conjunctival flap.[14]

The use of MMC is associated with side effects, including corneal oedema, delayed conjunctival epithelialization, scleral ulceration, scleral melt, anterior uveitis, iritis and cataract formation. Symptoms associated with the use of mitomycin C include ocular pain, photophobia and a foreign body sensation.[21] The pterygium recurrence rate after the use of MMC varies from 0% to as high as 40% when used with the bare sclera technique.[28]

5-Fluorouracil (5-FU) is an antimetabolite. It is a pyrimidine nucleoside analogue that interrupts cellular DNA and RNA synthesis. It blocks the formation of thymidylate synthase. It has the greatest effect on rapidly growing cells and also prevents fibroblast proliferation.[5] The proliferation of corneal epithelial cells, conjunctival fibroblasts and Tenon's capsule fibroblasts are inhibited by the administration of 5-FU.[14]

If administered intraoperatively, the 5-FU is applied to the bare sclera on a sponge after excision of the pterygium. A concentration of 25 mg/ml is used.[5] Postoperatively 5-FU can be administered as a subconjunctival injection. Recurrence rates after adjuvant 5-FU vary from 5 to 25%. The side effect profile includes local irritability. 5-FU has a lower side effect profile compared to MMC, with only mild or temporary symptoms reported after the use with pterygium surgery.[28]

Adverse events following the use of 5-FU related to glaucoma surgery is more common. These events include chronic epithelial defects, bacterial ulcers and filtering bleb rupture. In these glaucoma cases the dose of 5-FU used is usually up to 10 times higher than that used in pterygium surgery. A relative contraindication to the use of 5-FU is a known history of corneal pathology. This is due to the possibility of 5-FU causing aggravation of corneal disease, even if used at low dosages.[29]

Cyclosporine A is a calcineurin inhibitor that can be used to decrease inflammation. It is given postoperatively as a topical medication to decrease the risk of pterygium recurrence after excision biopsy. The concentration used varies from 0.05% to

01%.[30] Cyclosporine A causes selective suppression of T-Lymphocytes. T-Lymphocyte mediated cellular immunity appears to be actively involved in the pathogenesis of pterygium formation. Cyclosporine inhibits vascular endothelial growth factor triggered angiogenesis. The use of cyclosporine A is relatively safe and well tolerated by patients. However, contraindications include patients with known scleral thinning.[14]

Anti-vascular endothelial growth factor (anti-VEGF) levels in pterygium tissue have been found to be higher than in normal conjunctival tissue. Anti-VEGF has also been shown to be over expressed in recurrent pterygia. This suggests a link between angiogenesis, neovascularization and pterygium recurrence.[31]

The use of anti-VEGF could be effective in preventing recurrence. The use of anti-VEGF has been shown to decrease vascularization in pterygium tissue. This regression of neovascularization is only transient. This is probably due to the limited bioavailability of anti-VEGF.[32] When compared directly to MMC, the recurrence rate in the use of bevacizumab was 66% compared to the use of MMC at 26%.[33] The most commonly used anti-VEGF is the recombinant monoclonal antibody bevacizumab (Avastin, Genentech). Anti-VEGF can be administered intra-operatively or post-operatively as a subconjunctival injection.[5] There is a high cost associated with the use of anti-VEGF agents. This should be taken into account when deciding on the use of these agents, especially because of the transient action of neovascular regression.

Beta-irradiation was used historically to prevent pterygium recurrence. This was delivered through Ruthenium 106 or Strontium 90 sources. The radioactive plaque was usually applied to bare sclera until the treatment dose was reached.[5] Beta-irradiation is however, not without complications. These complications include ocular burning, foreign body sensation, corneal opacities, photophobia, conjunctival scarring, scleral necrosis, granuloma formation, cataract formation and in rare instances endophthalmitis.[14,34] The use of Beta radiation has decreased in popularity in modern surgery due to the risk of complications. Commonly used dosages in the treatment of pterygia include 25 Gray with bare sclera surgery and 10 Gray if a

conjunctival autograft is used.[35] Radiotherapy usually show the best results with fractionated doses, initiated within 24 hours of pterygium surgery.[14]

v) Complications of pterygium surgery

The most commonly encountered postoperative complications of primary pterygium surgery include graft oedema, graft necrosis, conjunctival inclusion cysts, granulomas of the Tenon's capsule, subconjunctival haematomas, scleral thinning, corneal narrowing, Dellen ulcers and pterygium recurrance.[5,20]

2. Aims

To find the prevalence and associated risk factors of pterygium recurrences in patients who underwent pterygium surgery at the Universitas Academic Hospital Complex.

3. Objectives

The objectives of this study were:

- To document the demographics of the study population
- To describe the prevalence of pterygium recurrence
- To outline the risk factors involved

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Chapter 2

1. Abstract

Aim: To find the prevalence and associated risk factors of pterygium recurrences in patients who underwent pterygium surgery at the Universitas Academic Hospital Complex.

Methods: A retrospective cross sectional study of all patients who underwent pterygium surgery at the Universitas Academic Hospital Complex between January 2016 and December 2018.

Results: A total of 117 eyes from 94 patients were identified. Most patients (83%) presented 6 months after noticing symptoms related to the pterygium including; redness (30%), tearing (13%) and foreign body sensation (10%). Inflammation was noted in 21% of patients. The most common surgical procedure performed was conjunctival autografts (74%), followed by conjunctival rotational flaps (10%), amnion grafts (10%) and bare sclera (2,5%).

Bare sclera technique was used in 3 cases, 2 of these (66,7%) had a recurrence. Conjunctival autografts were used in 86 cases, of these 10 cases (11,6%) had a recurrence. In 17 cases a conjunctival rotation flap was used, 3 patients (17%) had a recurrence. An amnion graft was used in 12 patients, 6 of them (50%) had a recurrence. The total recurrence rate was 21 (18%).

Conclusion: Compared to the bare sclera technique and amnion grafts, conjunctival autografts and conjunctival rotational flaps had lower recurrence rates.

2. Introduction

A pterygium is a degenerative condition of the eye. It is a wedge shaped growth consisting of fibrovascular tissue. It was described by the first recorded ophthalmic surgeon, Susruta, as early as 1000 BC.[1] It is continuous with the bulbar conjunctiva. The growth extends a variable distance onto the cornea. It usually presents bilaterally, on the nasal aspect of the eye. There is an association with exposure to environmental factors including dust, wind and ultraviolet (UV) light.[2]

There is a worldwide occurrence of pterygia, with a high prevalence around the “pterygium belt”. This is the area between 30 degrees north and 30 degrees south of the equator. The prevalence varies widely from 0,3% to 29% depending on the latitude. Increase in geographical latitude is related to a decrease in the prevalence of pterygium.[3]

The histological characteristics of a pterygium show a basophilic degeneration of the subepithelial substantia propria and stromal collagen fragmentation. This is also known as elastotic degeneration. Mild squamous metaplasia may be seen in the overlying epithelium. This is represented by a loss of goblet cells and keratinization of the surface.[4]

A pinguecula is similar to a pterygium in its location and origin. A pinguecula is a thickening of the bulbar conjunctiva, with the same histological characteristics as a pterygium. The distinguishing feature between the two is that a pterygium extends onto the cornea and has an absence of the Bowman’s membrane. A rupture in Bowman’s membrane results in a firm attachment of the pterygium to the underlying stroma. Pterygia present with an increase in mast cells.[5]

The pathogenesis of this disease is not yet fully understood, however certain risk factors have been identified. One of the main factors is Ultraviolet (UV) radiation exposure.[6,7] Other pathogenic factors include viral infections, epigenetic aberrations, inflammatory mechanisms**,** anti-apoptotic mechanisms**,** neo-angiogenic upregulation and hereditary predisposition.[8]

Pterygia are found in the palpebral fissure, growing from the conjunctiva onto the cornea. Pterygia grow towards the visual axis and can induce significant astigmatism. When inflamed, pterygia can cause ocular irritation. Patients may have complaints regarding the cosmetic appearance. Restrictive strabismus has also been described in severe or recurrent cases. Stocker lines (linear iron deposits) and Islets of Vogt (elevated white opacities) may be seen at the leading edge of an active pterygium.[9]

Surgery is the management of choice for pterygia causing visual disturbances. The main complication of pterygium surgery is recurrence. Currently, there is no single standardized surgical method recommended.[10] Chronic ocular irritations and decreased vision were included amongst the main indications for surgery.[11]

Early pterygium surgery included detachment and surgical excision of the pterygium head from the cornea. This was then modified into the bare sclera technique.[10] During the bare sclera technique, the lesion is removed from the cornea together with the peri-limbal conjunctiva. The remaining rim of conjunctiva is then sutured into the sclera to create a barrier preventing remnant pathological tissue from re-growing towards the cornea. The remaining sclera is left bare, to re-epithelialize from the surrounding conjunctival rim. This technique carries a high recurrence rate (24%-89%).[12,13] The bare sclera technique is simple to perform and is associated with a short surgical time.[8] Due to the high recurrence rate, other techniques have been developed to cover the scleral defect and install a barrier of normal conjunctiva to prevent regrowth.[10]

The conjunctival autograft technique requires harvesting a free conjunctival graft from the same or other eye of the patient. The graft is usually harvested from the para-limbal region.[14] This has the added advantage of providing normal stem cells to the limbal area where the pterygium has been excised.[10] Accurate measurement of the defect created by excision of the pterygium and the graft tissue can lower the rate of recurrence. A graft size that is slightly larger than the exposed sclera should be used.[15] The graft size can be measured with a caliper and marked by a marker. Normal saline or local anaesthetic can then be injected subconjunctivally to separate the graft from the Tenon's layer. It is vital to remove the Tenon's capsule from the harvested graft.[3] The graft should be handled carefully to prevent damage. Graft reversal should also be prevented while moving it into place. This graft is then secured to the exposed scleral bed in the area of the excised pterygium with either sutures or fibrin glue. The use of sutures to secure the conjunctival graft is associated with an increased surgery time.[16] Sutures are also associated with a number of complications. These complications include postoperative discomfort, inflammation, infection and suture granuloma formation. The use of fibrin glue can provide an alternative. Complications related to the use of fibrin glue include graft

dislocation. Autologous blood serum can be used as an alternative to fibrin glue. The recurrence rates for the conjunctival autograft technique varies between 3,3% and 13,5% for the primary procedure and up to 33,3% in cases of recurrent pterygium surgery.[8] Autografts are usually harvested from the superior temporal conjunctiva.[14] This can cause iatrogenic damage to the conjunctiva in that region. Up to 37% of patients can develop some form of scarring at the donor sight. This may have an influence on future glaucoma surgery.[17]

A conjunctival rotation flap can also be used. This is a relatively simple procedure with a shorter surgical time when compared to the free autograft.[18] The conjunctival rotation flap involves the mobilization of a conjunctival flap from the superior or inferior conjunctiva. This flap is then sutured to the defect created during the pterygium excision, thus creating a barrier of normal conjunctiva to block the recurrence of the pterygium.[10]

The amnion graft technique makes use of an amnion membrane. The amnion membrane consists of the inner layer of the placental membrane. It is made up of a basement membrane and an avascular stromal matrix. During surgery the amnion membrane is attached over the area of bare sclera with the basement membrane facing upwards. Sutures or fibrin glue can be used to secure the amnion graft.[8] Ocular surface inflammation plays a significant role in the recurrence of pterygia.[19] The effectiveness of amnion membrane grafts in pterygium surgery is due to the inhibition of pathological neovascularization, promotion of conjunctival epithelialization and the prevention of inflammation. It is effective in suppressing transforming growth factor beta (TGF-beta) signaling and the transformation of myofibroblasts in pterygia. The recurrence after amnion membrane grafting varies between 3,8% to 40,9%.[17] Advantages of using amnion grafts to cover the exposed sclera include shorter operating times and preserving the conjunctiva for future glaucoma filtering procedures.[20] Amniotic membranes are useful for covering extensive surgical defects in cases of large or combined medial and lateral pterygium removal.[8] When comparing amnion membrane grafts to conjunctival autograft, a lower recurrence rate is shown with the conjunctival autograft.[12,13]

Adjuvant treatment can be combined with all the above mentioned surgical techniques. Mitomycin C (MMC) is an alkylating agent. It inhibits mitosis, protein and DNA synthesis by DNA cross linking. It also inhibits fibroblast proliferation. It can be used intra and postoperatively. No standardized treatment protocol is currently available. The pterygium recurrence rate after the use of MMC varies from 0% to as high as 40% when used with the bare sclera technique.[21]

5-Fluorouracil (5-FU) is an antimetabolite. It is a pyrimidine nucleoside analogue that blocks the formation of thymidylate synthase. It has the greatest effect on rapidly growing cells and also prevents fibroblast proliferation. If administered intraoperatively, the 5-FU is applied to the bare sclera on a sponge after excision of the pterygium. Postoperatively 5-FU can be administered as a subconjunctival injection.[10] Recurrence rates after adjuvant 5-FU vary from 5 to 25%.[21]

Anti-vascular endothelial growth factor (anti-VEGF) levels in pterygia tissue have been found to be higher than in normal conjunctival tissue. This suggests that the use of anti-VEGF could be effective in preventing recurrence.[21] When compared directly to MMC, the recurrence rate in the use of bevacizumab was 66% compared to the use of MMC at 26%.[22]

Beta-irradiation was used historically to prevent recurrence. This was delivered through Strontium 90 sources. However, beta-irradiation is not without complications. The use of Beta radiation has decreased in popularity in modern surgery.[12]

The most commonly encountered postoperative complications of primary pterygium surgery include graft oedema, graft necrosis, conjunctival inclusions cysts, Tenon's capsule granulomas, subconjunctival haematomas, corneal narrowing, Dellen ulcers and pterygium recurrance.[10,17]

3. Methods

Study design

The study was a retrospective cross sectional study, conducted at the ophthalmology clinic at the Universitas Academic Hospital Complex.

Study population

The targeted study population were patients who underwent pterygium surgery at the Universitas Academic Hospital Complex between January 2016 and December 2018. The specific time period was chosen as the use of amnion grafts was introduced to the department at this time.

Study setting

All files were collected from the ophthalmology clinic. The theatre registry was used to identify the files of the patients who underwent pterygium surgery during the period from January 2016 to December 2018.

Sampling

No sampling was done. All primary pterygium surgery cases between January 2016 and December 2018 were included. The files of patients where the primary surgery was completed at another hospital were excluded.

Data Collection and Management

All the files of patients who received surgery for a pterygium at the Universitas Academic Hospital Complex were identified using the theatre register. Once identified the files were collected in the ophthalmology clinic by the researcher. The information (Appendix B) was then captured in an Excel format (Appendix A) by the researcher. The information was collected in duplicate to prevent data typing errors.

All data collection was done at the ophthalmology clinic. These Excel spreadsheets were sent to a statistician for analysis.

Data Analysis

Descriptive statistics, namely frequencies and percentages for categorical data and medians and percentiles for numerical data were calculated per group. The groups were compared by means of the One-way analysis of variance Kruskal-Wallis test for numerical data and the Chi-square test or the Fisher's Exact test for categorical data. The relative risk for recurrence was calculated and described by means of 95%

confidence interval for the relative risk. The prevalence of recurrence was calculated and described by means of 95% confidence interval for the prevalence.

The analysis was done by the Department of Biostatistics at the University of the Free State

Ethical considerations

The permission for the study was requested and conducted under the rules and regulations of the Department of Health (DOH) and the University of the Free State Health Sciences Research Ethics Committee (HSREC). The researcher alone handled the files and collected the data. No personal information was reflected on the data collected. All information collected was treated with confidentiality.

4. Results

Demographics

A total of 117 eyes of 94 patients who underwent pterygium surgery were identified for this study. These patients presented to the ophthalmology clinic at the Universitas Academic Hospital Complex and had their primary surgery completed at this hospital.

Table I – Demographics

Characteristics	n=number	%=percentage
Gender		
Male	23	20%
Female	94	80%
Laterality		
Right eye	60	51%
Left eye	57	49%

(Median age is 49 years, youngest 20 years, oldest 75 years)

As shown in Table I, the median age of these patients was 49 years. The youngest being 20 years and the oldest 75 years old. Of these patients 80% were female and 20% were male. The right eye (51%) was slightly more affected than the left eye (49%).

Clinical

Most patients (83%) presented more than 6 months after they started noticing symptoms related to the pterygium, with only 17% presenting within the first 6 months (Table II). The following symptoms were noted by the patients: redness (30%), tearing (13%) and foreign body sensation (10%).

Table II – Clinical data

Clinical presentation	n=number	%=percentage
Time of presentation		
More than 6 months	97	83%
Less than 6 months	20	17%
Clinical signs		
Medial	116	99%
Lateral	5	4%
Fleshiness	6	5%
Stocker line	1	1%
Inflammation	24	21%

In 99% of patients, a medial pterygium was observed and 4% presented with a lateral pterygium. Some cases presented with both medial and lateral pterygia. Inflammation was noted in 21% of patients.

Surgical Experience

Surgical experience was assessed based on the number of years that the registrar had spent in the department. This was divided into more or less than 2 years of experience. Surgeries that were performed by registrars with more than 2 years of experience were 47% of the cases, whereas surgeries performed by those less than 2 years were 53% (Table III).

Table III – Surgical experience

Years of experience	n=number	%=percentage
More than 2 years	55	47%
Less than 2 years	62	53%

Treatment

The patients were treated with one of four surgical options once the pterygium was removed. In 3 of the cases (2,5%) the sclera was left bare, with no further surgical closure. A conjunctival autograft was used to close the sclera in 86 cases (74%). In

17 cases (15%) a conjunctival rotational flap was used and 12 cases (10%) received an amnion graft to close the scleral defect

Adjuvant treatment was used intra-operatively in 31 cases (27%). None of the patients received MMC. Anti-VEGF was used in 29 cases (25%) and 5-FU was used in 2 cases (2%).

Recurrences

Recurrences were observed in 21 cases (18%) with a 95% confidence interval for recurrence of [12.0%; 25.9%]. Of these cases, 10 presented within 6 months (48%) and 11 presented after 6 months (52%). Surgical re-excision was performed in 8 of the recurrence cases (38,1%), while 10 (47,6%) received medical adjuvant therapy (Table IV). The remainder of the cases were either awaiting surgery or refused any further intervention.

Table IV – Recurrences

Characteristics	n=number	%=percentage
Time of recurrence		
Less than 6 months	10	48%
More than 6 months	11	52%
Treatment of recurrence		
Surgical Re-excision	8	38,1%
Medical adjuvant therapy	10	47,6%

The bare sclera technique was used in a total of 3 cases, 2 of these cases (66,7%) had a recurrence. A conjunctival autograft was used in 86 cases, of these 10 cases (11,6%) had a recurrence. In a total of 17 cases a conjunctival rotation flap was used, 3 cases (17%) had a recurrence. An amnion graft was used in 12 cases, 6 of them (50%) had a recurrence.

5. Discussion

This was a retrospective cross sectional study of recurrences of pterygia conducted over a 3-year period (January 2016 to December 2018) at the ophthalmology clinic at the Universitas Academic Hospital Complex. Results show that 80% of the patients who presented to the clinic with a pterygium were female. This contrasts the

literature that describes a male predominance due to outdoor work and UV exposure.[23] Most patients (83%) presented after 6 months of starting to notice symptoms. The following symptoms were noted by the patients: redness (30%), tearing (13%) and foreign body sensation (10%). Signs of inflammation were noticed in 21% of patients. A correlation between these signs and symptoms and the recurrence rate could not be found. Registrars with less than two years of experience performed 53% of the surgeries. No correlation between the experience of the registrar and the rate of recurrence could be found. The majority of the cases received a conjunctival autograft (74%). In this study the recurrence rate of this procedure was 11,6%. This is comparable to the recurrence rate described in the literature for the conjunctival autograft procedure varying between 3,3% and 13,5%.[8] A Chi-square was used to compare patients with a recurrence to the intra-operative use of a conjunctival autograft. This showed a relative risk of 0.602 in patients who received the conjunctival autograft. From this result, it can be concluded that the use of a conjunctival autograft protects against recurrence. Of the 12 patients who received an amnion graft, 6 of them (50%) had a recurrence. This recurrence rate was slightly higher than the described rate of 3.8% to 40.9% in the literature. Isolated studies including Essex *et al.* found a recurrence rate of up to 64% in amnion grafts.[24] The increased rate of recurrence might be explained by the small sample size in the current study. The use of an amnion graft was compared to patients with recurrences using the Fisher's Exact Test. This showed a relative risk of 4.571. Patients who received an amnion graft were shown to be 4.57 times more likely to have a recurrence in this study. The use of adjuvant intraoperative treatment, including 5-FU and anti-VEGF, did not show a correlation with the rate of recurrence. A total of 21 cases (18%) showed pterygium recurrence during the 3-year study period.

6. Conclusion

Due to the higher rates of recurrences in the use of the bare sclera and amnion graft techniques, the author recommends the use of a conjunctival autograft for cases elected to receive pterygium surgery. This is in order to reduce postoperative recurrences. Due to the small sample size of patients that received amnion grafts, further research is needed.

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Appendices

1. Letter of approval from Research Ethics Committee

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

23-May-2019

Dear **Dr Christian Engelbrecht**

Ethics Clearance: **THE PREVALENCE OF PTERYGIUM RECURRENCES AND ASSOCIATED RISK FACTORS AT THE UNIVERSITAS ACADEMIC HOSPITAL COMPLEX IN BLOEMFONTEIN**

Principal Investigator: **Dr Christian Engelbrecht**

Department: **Ophthalmology Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2019/0464/2506**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
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2. Permission from Department of Health

health
Department of Health
FREE STATE PROVINCE

15 May 2019

Dr. C Engelbrecht
Dept. of Ophthalmology
Faculty of Health Sciences
UFS

Dear Dr. C Engelbrecht

Subject: THE PREVALENCE OF PTERYGIUM RECURRENCES AND ASSOCIATED RISK FACTORS AT THE UNIVERSITAS ACADEMIC HOSPITAL COMPLEX IN BLOEMFONTEIN

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of the Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 15/05/19

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za

3. Permission from Head of Department

UNIVERSITY OF THE
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FREISTATA

UFS
UV

2019/02/26

Dr C Engelbrecht
Registrar
Department of Ophthalmology

THE PREVALENCE OF PTERYGIUM RECURRENCES AND ASSOCIATED RISK FACTORS AT THE UNIVERSITAS ACADEMIC HOSPITAL IN BLOEMFONTEIN

Your application to conduct the above mentioned research study in the Department of Ophthalmology, Universitas Hospital Annex is acknowledged.

I therefore confirm that permission has been granted for you to conduct the study.

Researcher: Dr C Engelbrecht, Registrar, Department of Ophthalmology.

Kind regards,

Prof Wayne J Marais
Head of Department
Department of Ophthalmology
University of the Free State
Bloemfontein

Tel: 051-405 2151
Fax: 051-430 2225
Email: wjmicu@gmail.com

4. Forms for collecting data

THE PREVALENCE OF PTERYGIUM RECURRENCES AND ASSOCIATED RISK FACTORS AT THE UNIVERSITAS ACADEMIC HOSPITAL BLOEMFONTEIN

Instructions

Data collection

Study ID number _____

Date of initial surgery (dd/mm/yy)……/……./…...

Patient details:

1	Age		
2	Gender	Male	Female
3	Laterality	Left	Right
4	Time of presentation	<6/12	>6/12

Symptoms:

5	Redness	Yes	No
6	Tearing	Yes	No
7	Foreign body sensation	Yes	No

Signs:

8	Medial	Yes	No
9	Lateral	Yes	No
10	Fleshiness	Yes	No
11	Stocker lines	Yes	No
12	Inflammation	Yes	No

Plan of surgery:

13	Surgeon experience	<2yrs	>2yrs

Type of Surgery:

14	Bare sclera	Yes	No
15	Conjunctival autograft	Yes	No
16	Conjunctival rotation flap	Yes	No
17	Amnion graft	Yes	No

Adjuvant treatments:

18	Mitomycin C	Yes	No
19	5-FU	Yes	No
20	Anti-VEGF	Yes	No

Recurrence:

21	Time of recurrance	<6/12	>6/12
22	Surgical re-excision	Yes	No
23	Medical aduvant therapy	Yes	No
24	Date of presentation of recurreace dd/mm/yy)……/……./……		

5. Instructions to authors of the named peer reviewed journal

Vol 13 | No 3 • Winter 2018
SA Ophthalmology Journal

South African Ophthalmology Journal guidelines for authors

The *SA Ophthalmology Journal* is a peer-reviewed scientific journal and the official mouthpiece of the Ophthalmological Society of South Africa. It appears on a quarterly basis.

1. A cover sheet is to be submitted with each manuscript. It should contain the title of the manuscript, the names of all authors in the correct sequence, their academic status and affiliations. The main author should include his/her name, address, phone and email address.

2. Articles should be the original, unpublished work of the stated author. All materials submitted for publication must be submitted exclusively for publication in this journal. Written permission from the author or copyright holder must be submitted with previously published figures, tables or articles.

3. The Editor reserves the right to shorten and stylise any material accepted for publication.

4. Authors are solely responsible for the factual accuracy of their work.

5. Articles should be between 2 000 and 3 000 words in length. A 200-word abstract should state the main conclusions and clinical relevance of the article.

6. All articles are to be in English and are to follow the Vancouver style.

7. Abbreviations and acronyms should be defined on first use and kept to a minimum.

8. Tables should carry Roman numerals, I, II etc., and illustrations Arabic numbers 1, 2 etc.

9. References should be numbered consecutively in the order that they are first mentioned in the text and listed at the end in numerical order of appearance. Identify references in the text by Arabic numerals in superscript after punctuation, e.g. ...trial.[13]

10. The following format should be used for references:

    Articles:
    Kaplan FS, August CS, Dalinka MK. Bone densitometry observation of osteoporosis in response to bone marrow transplantation. *Clin Orthop* 1993;294:173-78.

    Chapter in a book:
    Young W. Neurophysiology of spinal cord injury. In: Errico TJ, Bauer RD, Waugh T (eds). *Spinal Trauma*. Philadelphia: JB Lippincott; 1991: 377-94.

11. Articles are to be submitted by email to the Editor-in-Chief, Prof Nagib du Toit at the following email address: nagib.dutoit@uct.ac.za
    The text should be in MS Word. Pages should be numbered consecutively in the following order wherever possible: Title page, abstract, introduction, materials and methods, results, discussion, acknowledgements, tables and illustrations, references.

12. All figures, tables and photographs should also be submitted electronically. Each figure must have a separate self-explanatory legend. The illustrations, tables and graphs should **not** be imbedded in the text file, but should be provided as separate individual graphic files, and clearly identified. The figures should be saved as a 300 dpi jpeg file.
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13. Authors should declare any interests, financial or otherwise, regarding the publication of their article.

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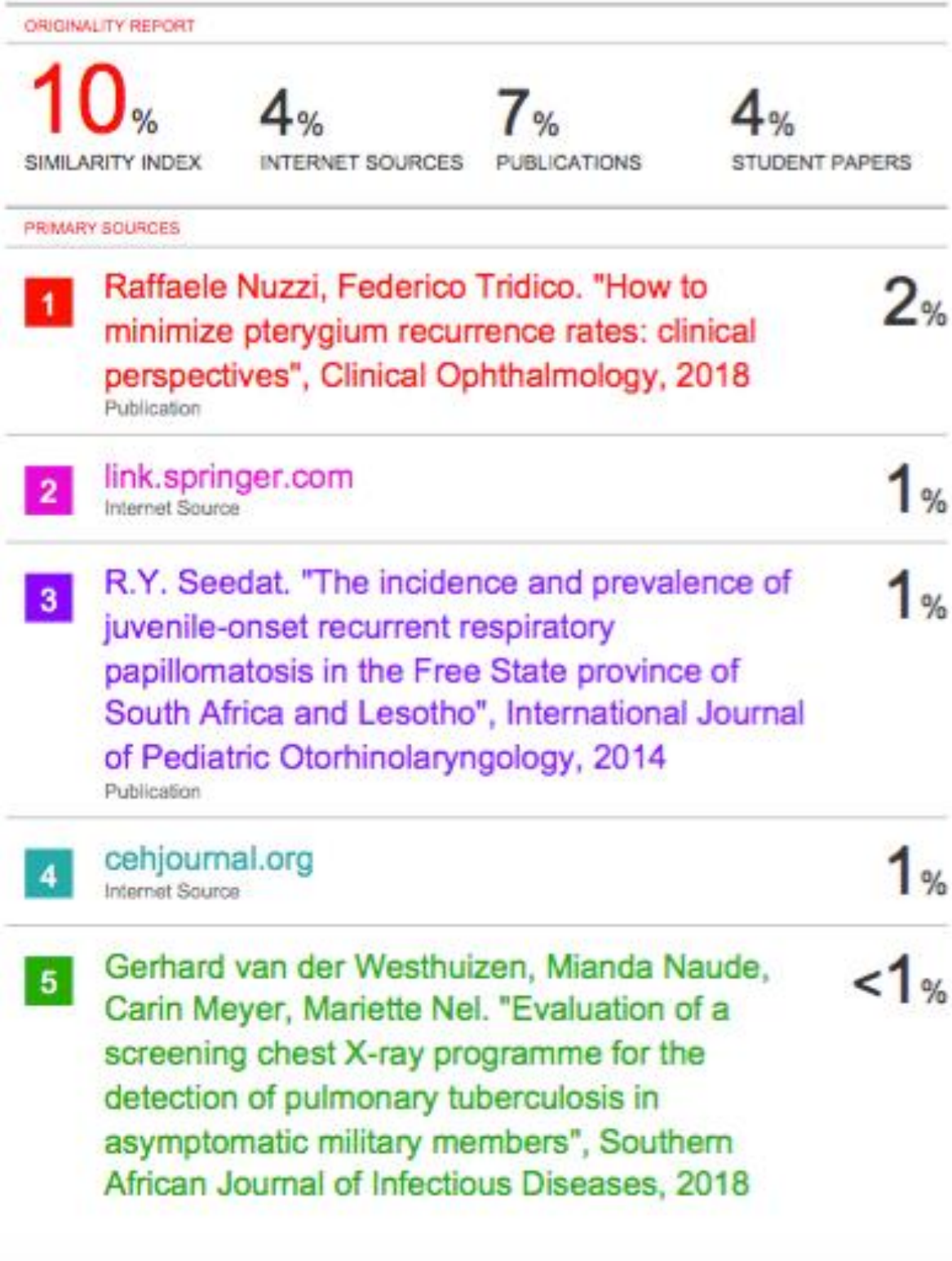

ORIGINALITY REPORT

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9	"Abstracts Programme", European Journal of Heart Failure, 2019 Publication	<1%
10	garuda.ristekdikti.go.id Internet Source	<1%
11	Submitted to Deakin University Student Paper	<1%
12	Submitted to University of Sunderland Student Paper	<1%

7. Copy of the research protocol approved by the HSREC

THE PREVALENCE OF PTERYGIUM RECURRENCES AND ASSOCIATED RISK FACTORS AT THE UNIVERSITAS ACADEMIC HOSPITAL COMPLEX IN BLOEMFONTEIN

MMED Protocol in Ophthalmology

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2) Literature Review

a) Introduction

A pterygium is a wedge shaped growth consisting of fibrovascular tissue, continuous with the conjunctiva. The growth extends a variable distance onto the cornea. It usually presents bilaterally, on the nasal aspect of the eye.[1]

b) Prevalence

There is a worldwide occurrence of pterygia, with a high prevalence around the "pterygium belt" between 30 degrees north and 30 degrees south of the equator. The prevalence varies widely from 0.3% to 29% depending on the latitude.[2]

c) Histology

A basophilic degeneration of the subepithelial substantia propria can be seen histologically. A pinguecula is a thickening of the bulbar conjunctiva, with the same histological characteristics as a pterygium. The distinguishing feature between the two is that a pterygium has an absence of the Bowman's membrane.[3]

d) Pathogenesis

The pathogenesis of this disease is not fully understood, however certain risk factors have been identified. These pathogenic factors include the following:

- Ultraviolet (UV) radiation
- Viral infections
- Epigenetic aberrations
- Inflammatory mechanisms
- Anti-apoptotic mechanisms
- Neo-angiogenic upregulation
- Hereditary predisposition.[4]

e) Clinical presentation

Pterygia are found in the palpebral fissure, growing from the conjunctiva onto the cornea. Pterygia grow towards the visual axis and can induce significant astigmatism. When inflamed pterygia can cause ocular irritation. Patients may have complaints regarding the cosmetic appearance. Restrictive strabismus has also been described in severe or recurrent cases. Stocker lines (linear iron deposits) and Islets of Vogt (elevated white opacities) may be seen at the advancing edge of an active pterygium.[5]

f) Treatment

Surgery is the management of choice for pterygia causing visual disturbances. The main complication of pterygium surgery is recurrence. Unfortunately, there is no single standardized surgical method recommended currently.[6] The methods of surgery that are widely used will be discussed below.

i) Bare sclera

This was the first technique adopted. In this technique the lesion is removed from the cornea together with the peri-limbal conjunctiva. The remaining sclera is left bare, to re-epithelialize from the surrounding conjunctival rim. This technique carries a high recurrence rate (24%-89%).[7] Due to the high recurrence rate other techniques have been developed to install a barrier of normal conjunctiva to prevent regrowth.[6]

ii) Conjunctival autograft

This technique requires harvesting a free conjunctival graft from the same or other eye. This graft is then secured to the scleral bed with either sutures or fibrin glue. The recurrence rates for this technique vary between 3.3% and 13.5% for the primary procedure and up to 33.3% in cases of recurrent pterygium surgery.[4]

The conjunctival rotation flap can also be used. This is a relatively simple procedure with a shorter surgical time when compared to the free autograft.[8] The conjunctival rotation flap involves the mobilization of a conjunctival flap from the superior or inferior conjunctiva. This flap is then sutured to the defect created during the pterygium excision.[6]

iii) Amnion graft

The amnion membrane consists of the inner layer of the placental foetal membrane. It is made up of a basement membrane and an avascular stromal matrix. During surgery the amnion membrane is placed over the area of bare sclera with the basement membrane facing upwards. Sutures or fibrin glue can be used to secure the amnion graft.[4]

Ocular surface inflammation plays a significant role in the recurrence of pterygia.[9] The effectiveness of amnion membrane grafts in pterygium surgery is due to the inhibition of pathological neovascularization, promotion of conjunctival epithelialization and the prevention of inflammation. It is effective in suppressing TGF-beta signaling and the transformation of myofibroblasts in pterygia. The recurrence after amnion membrane graft varies between 3.8% to 40.9%.[10]

iv) Adjuvant treatments

These can be combined with all surgical techniques.

Mitomycin C (MMC) is an alkylating agent. It inhibits mitosis, protein and DNA synthesis. It can be used intra- and postoperatively. No standardized treatment protocol is currently available.[11]

Fluorouracil (5-FU) is an antimetabolite. It is a pyrimidine analogue that inhibits thymidylate synthetase. It also prevents fibroblast proliferation.[6] This can also be administered intra- and postoperatively.

Anti-vascular endothelial growth factor (anti-VEGF) levels in pterygia tissue have been found to be higher than in normal conjunctival tissue. This suggests that the use of anti-VEGF could be effective in preventing recurrence.[11]

Beta-irradiation was used historically to prevent recurrence. This was delivered through Strontium 90 sources. Beta-irradiation is however not without complications. The use of Beta radiation has decreased in popularity in modern surgery.[6]

v) Complications of pterygium surgery

The most common postoperative complications of primary pterygium surgery include the following: graft oedema, graft necrosis, conjunctival inclusions cysts, granulomas of the Tenon's capsule, subconjunctival haematoma, corneal narrowing and Dellen ulcers.[10]

3) Research Question

What is the prevalence of pterygium recurrences and which associated risk factors were identified at the Universitas Academic Hospital Complex in Bloemfontein?

4) Aim

To find the prevalence of recurrences of pterygia after primary surgery and the associated risk factors involved at the Universitas Academic Hospital Complex.

5) Objective

The objectives of this study will be:

- To document demographics of the study population
- To describe the prevalence of pterygium recurrence
- To outline the risk factors involved

6) Methodology

a) Study design

The study will be a retrospective cross sectional study, conducted at the ophthalmology clinic at the Universitas Academic Hospital Complex.

b) Study population

Patients who underwent pterygium surgery at the Universitas Academic Hospital Complex between January 2016 and December 2018 will be included. Approximately 10 pterygium surgeries are performed at the Universitas Academic Hospital Complex per month. The specific time period was chosen as the use of amnion grafts was introduced to the department at this time.

c) Study setting

All files will be collected from the Ophthalmology clinic. The theatre registry will be used to identify the files of the patients who underwent pterygium surgery during the period from January 2016 to December 2018.

d) Sampling

No sampling will be done. All primary pterygium surgery cases between January 2016 and December 2018 will be included. The files of patients where the primary surgery was completed at another hospital will be excluded.

e) Data collection tools

Collected data will be captured using the Excel spreadsheet (Appendix A).

f) Data Collection

All the files of patients who received surgery for a pterygium at the Universitas Academic Hospital Complex will be identified using the theatre register. Once identified the files will be collected in the ophthalmology clinic by the researcher. The information (Appendix B) will then be captured in an Excel format (Appendix A) by the researcher. The information will be collected in duplicate to prevent data typing errors.

All data collection will be done at the ophthalmology clinic. These Excel spreadsheets will be sent to a statistician for analysis.

g) Data Analysis

Descriptive statistics namely frequencies and percentages for categorical data and means and standard deviations or medians and percentiles for numerical data will be

calculated per group. The groups will be compared by means of the appropriate statistical tests. The prevalence of recurrences will be calculated and described by means of 95% confidence interval for the prevalence. The analysis will be done by the Department of Biostatistics at the University of the Free State.

h) Ethical consideration

All information collected will be treated as confidential. The researcher alone will handle the files and collect the data. No personal information will be reflected on the data collection sheets. Informed consent will not be necessary as the data will be collected from patient records. Approval will be attained from the hospital CEO and the Department of Health of the Free State.

i) Pilot study

The data collection sheet will be evaluated for available data in files and ease of use. These will then be adjusted accordingly after review by an ethics committee member. Three files will be used to evaluate the collection sheet. These files used in the pilot study will later be re-analysed and included in the main study. The first file from each year of study will be analysed in the pilot study.

7) Measurements and Methodology

As this is a retrospective study there is a possibility that the information might be incomplete or missing. Data limitations include patients that received their initial surgery at another hospital as this study pertains to recurrences at the Universitas Academic Hospital Complex. All cases described as limitations will be excluded from the study.

Data integrity will be assured by typing the data into the Excel spreadsheet twice. This will then be verified before analyses.

8) Dissemination of findings

These will be published in appropriate peer reviewed journals and be presented at appropriate congresses. Feedback will be given to the Department of Ophthalmology to improve the management of this condition.

9) Timeline

Task	Duration
Protocol writing	January to February 2019
Ethics approval	March to April 2019
Data collection	April to June 2019
Data analysis	July to August 2019
Writing of thesis	September to November 2019

10) Budget

The budget for this research will be fully covered by the researcher:

Unit	**Cost**
Data for literature search	R250
Printing of thesis	R400
Total	**R450**

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