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THE ROLE OF MITOMYCIN-C (MMC) IN PRIMARY PTERYGIUM SURGERY FOR PREVENTION OF RECURRENCE

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ABSTRACT

Backgroud: Pterygium is a fibrovascular wing shaped, sub-epithelial fleshy ingrowth of bulbar conjunctival tissue which can spread to the corneal limbus and beyond. Pterygium is now accepted as a distorted wound-healing response and dys-regulated cell proliferation disease rather than a degenerative lesion. The stromal overgrowth of fibroblast and blood vessels is accompanied by an inflammatory cells infiltrate and accumulation of abnormal extracellular matrix. Pterygia are relatively common in the general population and typically follow an indolent course. It is a common health problem in Iraq because of dry hot climate. Simple excision of the pterygium alone has a very high recurrence rate. Many adjunctive methods have been used to reduce the recurrence such as chemical agents like mitomycin-C (MMC). The mechanism of action of MMC seem to inhibit fibroblast proliferation at the level of the episclera. The aim of study was to evaluate the effect of intraoperative MMC 0.04%(0.4 mg/ml) for 3 minutes on pterygium recurrence and complications after surgical removal with the bare sclera resection (BSR) technique. **Patients And Methods:** Prospective non-comparative interventional study was conducted at Eye unit, Alyarmouk Teaching Hospital. Fifty patients with primary nasal pterygium were selected. Detailed history was taken. Complete ocular examination done and those fulfilling inclusion criteria were applied in the study. We used topical proparacaine 0.5% and local infiltration of 2% lidocaine with 1:200.000 adrenaline, to all patients freshly prepared MMC 0.04% (0.4mg/ml) for 3 minutes was applied through a sponge spear at the bare part of the sclera then the eyes were thoroughly rinsed with a 100ml sterile balanced salt solution (BSS). Average surgery time was 20 minutes (range: 15–25min). All patients received topical corticosteroid and antibiotic treatment for at least 4 weeks postoperatively. All patients were followed for a minimum of one year and recurrence rates and complications were assessed after 3, 6, 9, and 12 months. Recurrence defined as fibrovascular tissues invading the cornea 1mm or more. **Results:** We recruited 50 eyes of 50 patients, 33 female patients and 17 male patients, with 26 right and 24 left eyes. Age range from 21-60 years, mean age at operation was 42.55 years. The size of pterygium on cornea was 2-5mm. Average surgery time was 20 minutes (range: 15–25min). Recurrence was defined as 1 mm fibrovascular tissue over the corneascleral limbus onto clear cornea in the area of previous pterygium excision. Two recurrent cases encountered (recurrence rate 4%), one male after 3 months and another female after 6 months, the mean is 4.5 months. The side effects encountered were: ocular discomfort, phtophobia, lacrimation, foreign body sensation, and ocular pain in 35 cases(70%). Chemosis, oedema & hyperemia of surrounding conjunctiva in 30 cases (60%). Superficial punctate keratitis in 2 cases (4%). Conjuctival avascularity in areas of pterygium excision in 15 cases (30%). Avascularised sclera in 25 cases(50%) between 1-6 months postoperatively. Granuloma in one case after 1 month (2%). The adverse side effects were all mild, self limiting, and easily treated. No patients experienced severe complications during 1 year of postoperative follow-up. **Conclusion:** A single intraoperative application of 0.04% (0.4mg/ml) MMC for 3 minutes after BSR technique of pterygium is associated with minimal complication and effectively reduces the recurrence rates. We prefer BSR technique followed by intraoperative MMC which was safe,simple and acceptable adjuvant for prevent recurrence, in comparism to MMC eye drops postoperatively in which the risk of overuse from self-administration of this toxic chemotherapeutic agent by the patients themselves at home, and postoperative therapy entails repeated bathing of the entire ocular, nasolacrimal, and oropharyngeal surfaces for 5–14days with MMC which carry high serious side effects and also prefer to another technique like conjuctival autograft (CAG) which is technically more difficult, time consume and inapplicable in cases with previous conjuctival disturbance.

KEYWORDS: bare sclera resction (BSR), blanced salt solution(BSS), conjuctival autograft (CAG), mitomycin-C (MMC), intraoperative(IO), postoperative(PO), pterygium, recurrence, ultraviolet (UV).

INTRODUCTION

A pterygium (from the Greek, pterygion, "small wing") is a wing-shaped, benign fibro-vascular, fleshy growth that originates on the conjunctiva and that can spread to the corneal limbus and beyond.[1] Pterygium was first described in 1000 BC by Sushruta, an Egyptian physician, is the first ophthalmic surgeon according to the literature, thought that pterygium was caused by a deficient nutrition.[2] In 460 B.C. Hippocrates described pterygion (a small wing). Majority of pterygium occurs in the nasal side, but it is not uncommon to encounter double-head pterygium in the "pterygium belt" region.[3] Pterygium is one of the most common conjunctival disease among ophthalmic pathologies. Pterygium is a common health problem in Iraq because of the hot, dry & dusty climate and simple excision of the pterygium alone has a very high rate of recurrence. It is more frequent in areas with more ultraviolet radiation(UVR)[4], especially UVR-A and UVR-B (290-400nm) which is considered the most dangerous.[5],[6] Various risk factors have been suggested, including enviroment, race, age, social status, occupation, educational background & a hereditary factor.[9],[10] A large North American study has reported pterygium to be almost twice as frequent among persons who worked outdoors but was only one-fifth as likely among those who always used sunglasses outdoors.[11] Outdoor work as a risk for pterygium development has also been reported by a study in 2012 by Ang et al.[12] Sunlight exposures (on an average of 1 h or more daily) were strongly associated with a higher risk of developing pterygium in people working outdoors.[13] Pterygium is a common disease in tropical and subtropical regions with a worldwide prevalence of 2%–7%.[14] It is also more frequent in hot, dry, windy, dusty and smoky environments which give rise to chronic irritation of the conjunctiva.[15],[16],[17],[18] Pterygium is a world wide condition with a "Pterygium belt" between the latitudes of 30 degree north and south of the equator mainly in people work in outdoor places**.** UVR light exposure may not be the only factor associated with the development of pterygium. Dust and sand may contribute to the development of pterygium. This could be explained by the fact that the normal flow of tears is from out inwards carrying with them any dust particles or fine foreign bodies as sandy dust is coarse than fine dust thereby exciting the inflammatory response with consequent formation of pterygium. Educational interventions to modify these potential exposures may assist in preventing pterygium. Wearing sunglasses or hats to avoid direct sun exposure to the eyes seems to have a protective effect.[17],[18] Several theories attempted to clarify its cause, but its pathology is still unexplained. Environmental factors play a significant role, especially in people who work in direct sunlight or under windy or extremely bright conditions or live in regions with high snowfall levels because of the reflective nature of fresh snow. Some individuals or occupations are more susceptible as farmers, drivers, welders, soliders and carpenters (outdoor work), welders & backers of bread exposed to flame (indoor work) mainly females as demonstrated in our study.[4],[19],[20],[21] Pterygium can be divided into three recognizable parts: the apex (head), neck, and body/tail. The apex or leading edge is a flat zone on the cornea that consists mainly of fibroblasts that invade and destroy Bowman's membrane. The raised triangular portion of the pterygium with its base toward the canthus is the body /tail is the mobile area of the bulbar conjunctiva, which can be easily dissected from the underlying tissue[23], the neck that includes the superficial limbus, whereas the head invades the cornea and forms the apex of the triangle.[24] A subepithelial cap or "halo"is present in front of the head of the pterygium[25], and is usually the first sign of pterygium.[26],[27] Stocker's line, which is iron deposition in the basal layer of corneal epithelium anterior to the cap, indicates that the pterygium is chronic**.**

PATHOGENESIS

The knowledge regarding the pathogenesis of pterygium has expanded vastly. Before now, early theories have proposed that pterygium development was associated with specific lifestyles such as outdoor working, exposure to sunshine, or dust. This led to the idea that chronic ocular surface irritation by such environmental factors might be the cause of the condition.[28] It was also proposed that pterygium arises from other sunshine related conditions, such as pingueculum. Pingueculum has no growth potential per se but may become inflamed and can evolve into a true pterygium.[29] Pterygium is now accepted as a distorted wound-healing response and dys-regulated cell proliferation disease rather than a degenerative lesion.[30] Apoptotic mechanisms[31], cytokines**,**[32] growth factors, angiogenic factors[33], viral infections, and heredity[34]**,** have been proposed as current causative agents in its pathogenesis and UVR exposure is known to induce their proinflammatory aspects.[8] Chronic irritation coupled with actinic damage are likely responsible for the fibrovascular reaction typical of pterygium. The stromal overgrowth of fibroblast and blood vessels are accompanied by an inflammatory cells infiltrate and accumulation of abnormal extracellular matrix.[22]

Some studies have shown that pterygium shares some similarities with cancers, because active cell proliferation occurs with minimal apoptosis.[35], [36] Pterygium also displays other tumor-like properties, such as invasion of cornea and its high recurrence after surgical excision. It also exists with secondary premalignant lesions. These tumor-like properties suggest that pterygium is possibly a premalignant tissue.[30],[37] Several studies also showed that the pathogenesis of pterygium is closely linked to the p53 gene mutation.[38] Thus, pterygium is considered the result of uncontrolled cellular proliferation, like a tumor.

CLINICAL PRESENTATION

Pterygium arises in the interpalpebral fissure as an elevated, fleshy mass on the bulbar conjunctiva near the limbus in its early stage. Engorged radial blood vessels

may appear over the pterygium and adjacent conjunctiva and usually signal a period of rapid growth. The bulbar conjunctiva may become increasingly taut as the pterygium enlarges toward the limbus. The complaints which it may give rise are foreign body feeling, burning, irritation, lacrimation, affects visual acuity by either involving visual axis or inducing astigmatism either with or against the rule as sectoral corneal steepening occurs. Lesions larger than 3.5 mm (more than halfway to the center of the pupil in a typical cornea) are likely to be associated with more than 1 D of astigmatism and often cause blurring of uncorrected vision.[39], [40], [41] Pterygium may also be a source of congestion and cosmetic problems.[42] As the apex approaches the visual axis, glare and decreased contrast sensitivity appear. In severe cases, symblepharon formation may limit ocular motility and result in diplopia. The lesion may remain quiescent for the remainder of the patient's life or resume growth again at a later time. Older, static lesions are often associated with an arcuate line of iron deposition in the superficial cornea immediately central to the cap known as Stocker's line.

TREATMENT

The treatment of pterygium can be conservative, medical, or surgical. Conservative treatment is indicated when symptoms are mild and usually involves avoidance of smoke, sun, wind, flame and dust-filled environment. Use of ultraviolent blocking glasses has been advocated by some authors in preventing progression.[43]

Medical treatment

Is used to relieve symptoms and involves use of topical, preservative-free lubricants, vasoconstrictors, and mild corticosteroids, have an important role in minimizing the patients discomfort but do not cure the disease. If the lesion grows, surgical intervention becomes more compelling.

Surgical treatment

Surgical treatment is indicated when significant discomfort, cosmetic disfigurement and functional problem in the form of reduced visual acuity, diplopia and problems in contact lens fitting are the major indications of surgery. The first report of a surgical treatment of pterygium is more than 3000 years old.[44] Many variations of this procedure since that time have been published. Only the BSR, with adjunctive therapy by MMC, was discussed in this study.

BSR technique: This is the most popular method for the removal of primary pterygium and was first described by D'Ombrain in 1948.[45] This technique involved the complete excision of the pterygium head and removal of some of the adjacent normal nasal bulbar conjunctiva along with excision of the underlying Tenon's capsule tissue, which then resulted in a bare sclera. Many ophthalmologists prefer to avulse the head from the underlying cornea. Advantages include quicker epithelialization, minimal scarring and a resultant smooth corneal surface.[23] The BSR involves excising the head and body of the pterygium while allowing the bare scleral bed to re-epithelialize. This technique was associated with a high recurrence rate (30%–88%)[29], [46] ,[47],[48] [49], [50],[51], and there is a higher risk of recurrence after re-excision of recurrent pterygium compared to a primary pterygium.[29],[46],[47],[52],[53],[54],[55],[56]

Surgical trauma and subsequent postoperative inflammation activate proliferation of subconjuctival fibroblasts and vascular cells, and deposition of proteins in turn contributes to the pterygium recurrence.[57] Removal of recurrent pterygium is more difficult due to corneal thining, symblepharon, and extention of the scar tissue to recti muscles.[58] In an effort to reduce the recurrence rate, adjunctive therapy such as, MMC has been used.[59]

MMC

Kunimoto N, Mori S. in 1969 in Japan[60], were the first to report the promising effect of MMC on the recurrence of pterygium. Singh et al introduced the use of MMC, as an adjunct to pterygium surgery, to Western ophthalmology in USA in 1988.[61]

MMC is an antineoplastic/antibiotic, anti-metabolite agent with anti-proliferative effect on cells showing the highest rate of mitosis. MMC isolated from the soil bacterium Streptomyces Caespitosus. The chemical formula is C15H18N4O5. It is an alkylating agent that is bio-reductive because it undergoes metabolic activation through a cytochrome P-450 reductase mediated reaction to create an alkylating agent it leads to the death of cells caused by the inability to repair the genotoxic injury caused by alkylation. It acts against all cells regardless of the cell cycle and even acts in cells that are not synthesizing DNA. Inhibition of DNA synthesis leads to reduction in the number of mitoses, especially when MMC comes into contact with cells that are in the late G1 and early S phases of the cell cycle. MMC damages cells by crosslinking DNA, forming covalent bonds with the guanine in DNA. MMC inhibits the synthesis of DNA, RNA, and protein in rapidly growing cells and is radiomimetic in many of its actions.[61], [62]

Its significantly reduces the rate of pterygium recurrence following its excision by inhibiting the proliferation of fast growing cells, such as fibroblasts and vascular endothelial cells in the episclera region.[67] The administration of MMC in the pterygium surgery is considered off-label by the Food and Drug Administration (FDA), but it is used in cancer treatment. Some studies with primary pterygium determined that all intraoperative MMC concentrations from 0.02% to 0.04%, given for 3 to 5min, reduced significantly the recurrence of pterygium when compared to excision with BSR.[48],[63],[64] Therefore, to reduce the risk of the recurrence, application of a single dose intraoperative MMC after the excision of the pterygium has been advocated by most authors.[49],

[50],[51],[52],[53],[54],[55],[56],[65],[66],[67]

The blood supply to pterygium mainly comes from the surface conjunctiva[68], and the usage of MMC following BSR can reduce the rate of recurrence in part because it can suppress neovascularization.[69]

MMC was first used topically at a concentration of 0.04% (0.4 mg/ml) eye drops three times daily for 1 to 2 weeks after pterygium surgery, with no recurrences by Kunimoto and Mori in 1969.[60] Other reports have confirmed the usefulness of MMC in pterygium surgeries with a recurrence rate ranging from 2% to 16**%.**[70],[71], [72]

Drug reconstitution and pharmacokinetics

MMC prepared by diluting lyophilized powder with BSS at neutral pH. The drug is available in a vial (2mg and 10mg). It is further reconstituted with BSS either 5 ml for 2 mg vial to make 0.4 mg/ml(0.04%) solution or 10 ml for 2 mg vial to make 0.2 mg/ml(0.02%) solution.[73] It has high bio-availability in the target tissue because of its hydrophobic character which favors its penetration into the epithelially denuded cornea and conjunctiva, while deterring its movement into or through intact epithelium.[60] MMC is inactivated in an acidic solution. The drug should be stored under refrigeration to preserve its potency under these conditions, MMC is potent for a period of two weeks.[73]

Complications of MMC

Photophobia, ocular pain, lacrimation, foreign body sensation (secondary to superficial punctate keratitis) and eyelid edema are cauntable as minor complications of topical MMC. The increased concentration and duration of the application may be associated with complications such as necrotizing scleritis, scleral calcification & ulceration, corneal edema, iritis, glaucoma, cataract, hypotony by injury of the ciliary body and damage to the corneal epithelium and endothelium, endophthalmitis, iridocyclitis and symblepharon were rare as a major complications of intraoperative topical MMC.[73],[74]

Contraindications for topical use of MMC

One-eyed patients, pregnant women, very old patients, severe dry eye, those with predisposing condition to corneal ulceration or poor healing such as immunocompromised patients or patients with Sjogren's syndrome, atopic keratoconjunctivitis, acne rosacea or herpetic keratitis.[73]

Two forms of MMC are currently used: the intraoperative application of MMC directly to the scleral bed after pterygium excision, and the postoperative use of topical MMC eyedrops. Several studies now advocate the use of only intraoperative MMC to reduce toxicity as we do in our study.

PATIENTS AND METHODS

A prospective non-comparative interventional case series study was carried out at the Department of Ophthalmology, Alyarmouk Teaching Hospital. Fifty cases following informed consent were registered, 17 were men and 33 women of primary nasal pterygium (26 right, 24 left), mean age was (42.55) years, range from 21–60 years,. The patients were inquired especially about their age, occupation and ocular symptoms. Complete ocular examination, extraocular movements, biomicroscopy, documentation of pterygeal size and dilated fundoscopy was performed to assure that none of them had major eye disease. The size of the pterygium, measured by the limbus – apex distance, was on average 4.5 mm (range 3–6 mm). Patients were operated through BSR technique, were treated with topical intraoperative MMC 0.04% (0.4mg/ml). All patients were followed for 12 months to assess the recurrence rate and complications.

Inclusion criteria

Age between 21-60 years, both sexes, primary nasal pterygium encroaching 2mm or more over the cornea, pterygium causing decreased vision, pterygium with repeated episodes of congestion and grittiness.

Exclusion criteria

Systemic: diabetes mellitus, pregnancy, collagen vascular disease or other autoimmune disease.

Ocular: only eye, recurrent pterygium, double head pterygium, dry eye syndrome, ocular infection, previous limbal surgery, keratitis sicca, Sjo¨gren syndrome, neurotrophic keratitis, acne rosacea, severe meibomian gland dysfunction, blepharitis, previous ocular surgery, longterm application of ocular medications, contact lens wear, cicatrical pemphigoid, glaucoma, cataract or vitreoretinal disease.

Operation

BSR technique: This is the most popular method for the removal of primary pterygium and was first described by D'Ombrain in 1948.[45] This technique was associated with a high recurrence rate (30%– 88%).[45],[61],[76] And there is a higher risk of recurrence after re-excision of a recurrent pterygium compared to a primary pterygium.[56] Therefore, this technique has been modified to reduce the recurrence rate**.** Those fulfilling inclusion criteria were operated under operating microscope. After preparing and draping the eye in normal sterile fashion, cleaning the lids and conjunctiva by 10% povidone- iodine solution, 0.5% proparacaine eye drop was dripped onto the conjunctiva for anesthesia. The lids were opened using a rigid eye speculum. Cautery spots are used to delineate the involved area of conjunctiva to be excised. Hydroxypropyl methylcellulose ophthalmic solution 2%(2ml) was applied on cornea to protect the cornea from dryness & to facilitate the dissection of head of pterygium from cornea by No.15 Baird –Parker blade. Lidocaine 1 ml of a 2% solution, with adrenaline 1:200.000 was injected into the pterygium to elevate it into its attachment to the cornea. The head of the pterygium was grasped with St Martin's toothed forceps

and excision was begun with a No. 15 Baird-Parker blade about 0.5 mm ahead of the pterygium and carried down clearly to the limbus. The conjunctiva and subconjunctival tissue (Tenon's capsule) are bluntly and meticulously dissected, the body of the pterygium was excised using spring-action scissors fellow the cautery spots which delinated before, were then cleaned over the sclera towards the insertion of the medial rectus muscle leaving 2–3 mm of bare sclera.[57] Haemostasis was assured with light bipolar cautery. No conjunctival sutures were used. Before application of MMC, use sponge spear tip to dry bare sclera. MMC was prepared by adding 5ml of BSS in 2mg vial, MMC 0.4 mg/ml (0.04%) by Merocel sponge spear soaked in the desired concentration applied intra-operatively over bare sclera for 3 minutes. The site of application was then thoroughly irrigated with at least 100 ml of BSS. Surgery time was 20 minutes (range 15–25). The MMC was prepared by adding 5 ml of BSS in 2 mg vial.

Here, we chose 0.04% and 3 minutes to have maximum efficacy with a reasonable safety. Postoperative topical combination of steroid and antibiotic ointment was used and pad was applied for 24 hours.

Postoperatively systemic ciprofloxacin 500mg tablet 1X2, analgesic tablet 1X3, topical antibiotics & steroid eye drops & ointment were used until epithelization was complete. Steroid and antibiotic drops were used 4 times daily for 1 month and ointment at night before sleep. Follow-up visits were scheduled for post operative days 1,7,15, 30,90, and then every 3 months. The recurrence was defined as post operative fibro- vascular re-growth crossing the corneo-scleral limbus by 1.0 mm or more and this constituted treatment failure and the follow-up was discontinued when the diagnosis of recurrence was established.[50] Primary outcome measures were, recurrence onset and complication. The application of MMC has two important goals: 1. Reduce recurrence because the source of recurrence is the subconjuctival tissue and 2. Improve the cosmetic appearance.

At each visit patients were examined for the presence of corneal epithelial disorders, punctate keratitis, anterior chamber reaction, recurrence, patients complaints such as pain, irritation, watering, and photophobia were recorded. All the recurrent cases did not undergo further pterygium operations and were managed conservatively according to the patients' preference. No severe complication was observed, oedema and hyperemia of surrounding conjunctiva was noted, which subsequently disappeared within 15 days. All patients were followed for a minimum of one year and recurrence rates and complications were assessed for 3, 6, 9, and 12 months. In all patients the avascularity zones were observed within the first postoperative months. In all these patients the overlying conjunctiva looked clinically normal except for a lesser vascular density over the bleached areas. Regarding demographic results of 50 patients, 30% between 21-40 years and 70% of patients age between 41-60 years. 33 females were age range from 21-60 years, the mean age was 37.9, female age from 21-40=26% and from 41-60=40%. 17 males, age range 30-60 years, the mean age was 47.2, male age from 30-41=4 % and from 41-60=30%. So most of patients in male & female more than 41 years. In table 2 & 3 shows types of occupations and shows percent of outdoor occupations more than indoor occupations. Table 5 shows the the recurrence in 2 patients (4%) one male and another female.

Table 1: Gender Age Distribution & Laterality.

No.of eyes	Age range (Years)	Mean Age (Years)	Female No.	Male No.	Laterality	
					Right	Left
50	21-60(100%)	42.55	33(66%)	17(34%)	26 (52%)	24(48%)
		Female:37.9				
		Male:47.2				
15	21-40(30%)					
35	41-60(70%)					
15	21-40	Female:35.5	13(26%)	2(4%)		
		Male:34				
35	41-60	Female:50.35	20(40%)	15(30%)		
		Male:49				

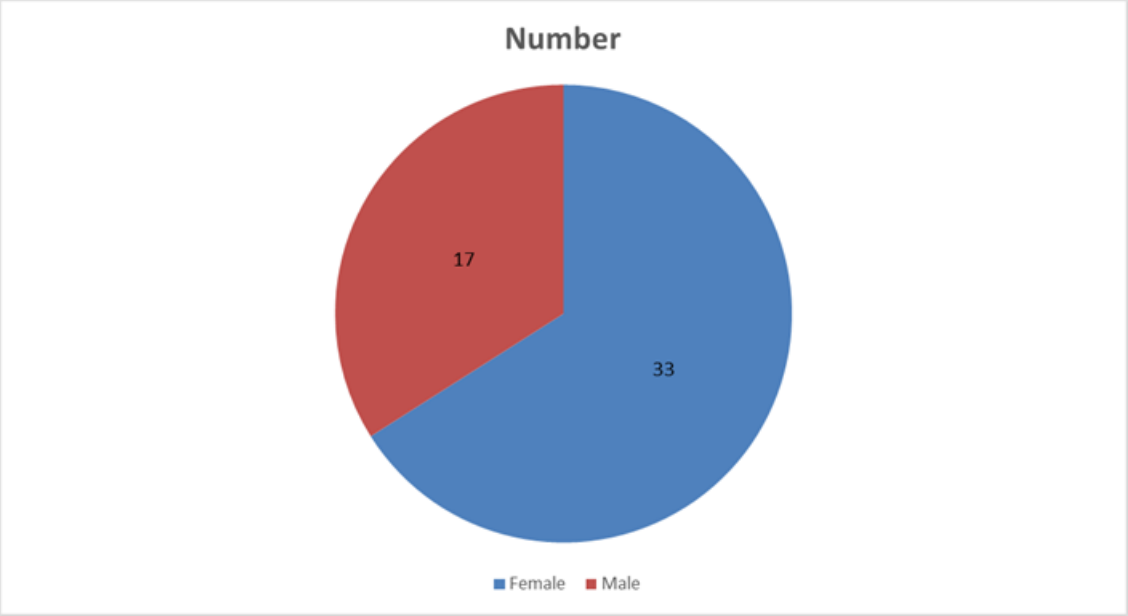

Fig. 1: Gender variation.

Table 2: Occupations of patients.

Occupation	Number of male(%)	Number of female(%)
Taxi driver	4(8)	-
Farmer	3(6)	19(38)
Labourer	3(6)	-
Baker	1(2)	14(28)
Welder	2(4)	-
Smith	1(2)	-
Motorcycle driver	1(2)	-
Carpenter	2(4)	-
Total	17(34)	33(66)

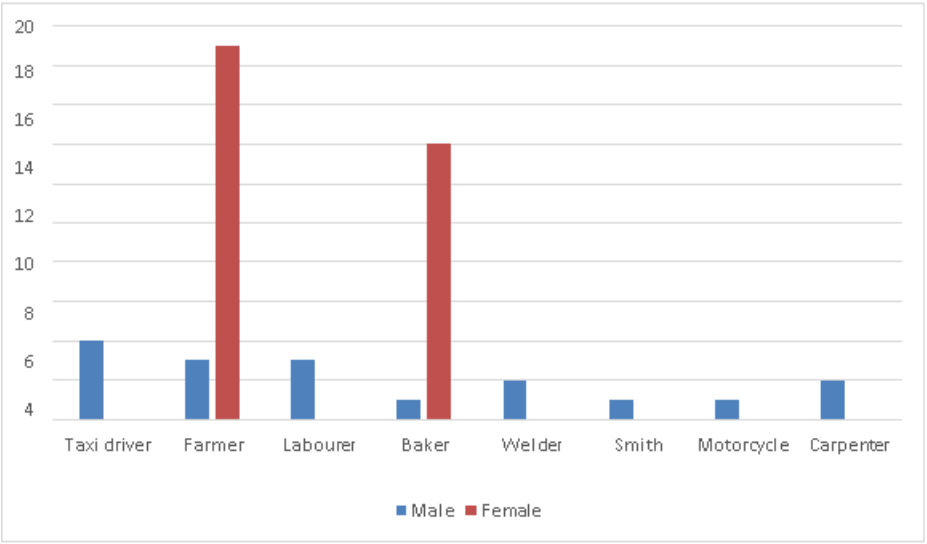

Fig. 2: Gender Occupation variation.

Table 3: Clinical data of outdoor & indoor patients.

Type of Occupation	No.(%)
Outdoor	30(60)
Indoor	20(40)
Total	50(100)

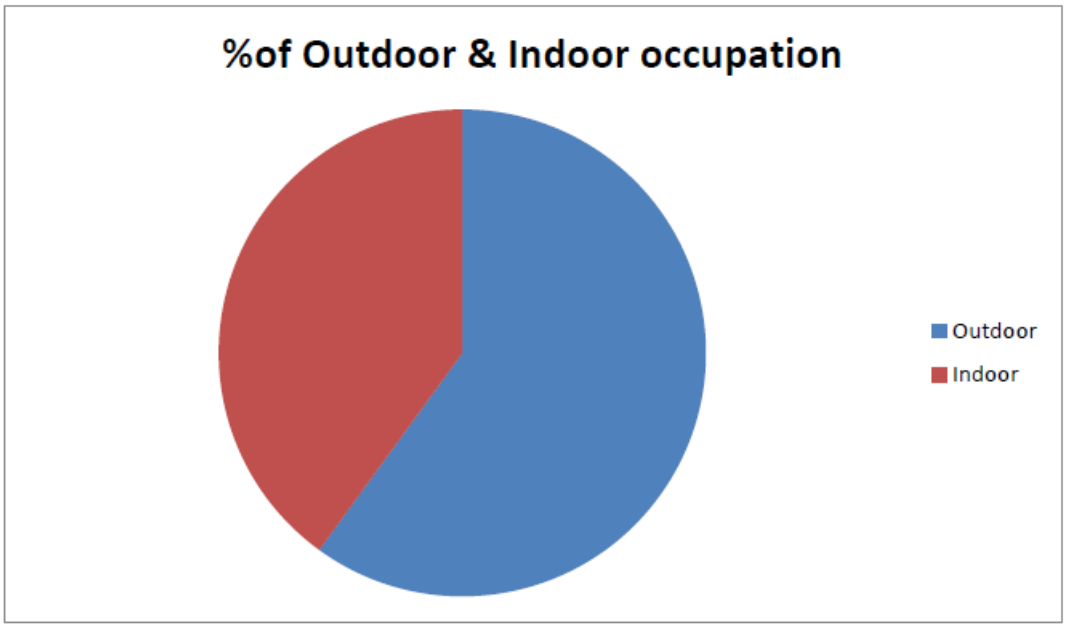

Fig. 3: Outdoor & Indoor variation.

Table 4: Showing postoperative complications in male & female.

Complication	No.(%)	Male	Female
Ocular discomfort, phtophobia and lacrimation, foreign body sensation, and ocular pain	35(70)	20	15
chemosis, oedema & hyperemia of surrounding conjunctiva	30(60)	16	14
Superficial punctate keratitis	2(4)	1	1
granuloma	1(2)	1	0
Conjuctival avascularity	15(30)	5	10
Avascular sclera	25(50)	10	15
Recurrence	2(4)	1	1

Table 5: Showing incidence of recurrence.

Post operative period	Patients Gender(%)	Gender %
3 months	1 male(2)	5.8%
6 months	1 female(2)	3%
Total	2	4%

RESULTS

Fifty patients had primary pterygium located nasally, were operated on with a one year follow up. 33 patients were females(66%) and 17 patients were males(34%) as shown in table1. Thus female to male ratio was 2:1. The age of the patients ranged from 21-60 years, mean (42.55years), regarding gender variation, female age range was 37.9years, in male was 47.2years, regarding laterality nearly the same number. The number of patients more in female than male may be due to aesthetic complaints more in females. Surgery time was 20min (range 15–25minutes). In all the patients, photophobia, lacrimation, foreign body sensation, and ocular pain were resolved between the first week and 2 week following surgery. Conjunctival reepithelialization occurred within 2 weeks in all the patients. A postoperative granuloma occurred in 1 patient as shown in table 4. It was treated with topical steroids. All the patients had corneal reepithelialization within the first 2 weeks following the surgery. No other ocular or systemic complications were observed. Recurrent pterygium developed in 2 eyes (4%) as shown in table 5.

Recurrence was defined as regrowth of conjunctival fibrovascular tissue, encroaching into the corneal limbus more than 1 mm. All recurrences occurred within 6 months, one within 3 months (male), and the other within 6 months (female). The recurrence rate was 4%; 5.8% in male and 3% in female. The mean recurrence time was 4.5 months (range 3–6 months).

Most complications were transitory and mild as shown in table 4. All patients had a burning foreign body sensation about one week after surgery. They were all satisfied with the cosmetic result. The tendency to ‘‘red eye’’ had diminished. At the first-month visit complete re-epithelization had occurred with a smooth conjunctival scar. There were two patients with punctate epithelial keratits were treated with lubricant and resolve within 2 weeks. No complications such as corneal and

conjunctival epithelial defect, scleral thinning, necrosis, perforation or corneal melting, medial rectus disinsertion, glaucoma, iritis, chronic pain or any other visually significant complication was encountered. In our study the pterygium was common in outdoor workers (60%) and less in indoor workers (40%) as shown in table 3 & fig.3.

DISCUSSION

Pterygium surgery has been a challenge in the past, because of high recurrence rate, the BSR technique alone proved unsatisfactory, today some specific techniques and adjunctive treatments following surgery are used in order to decrease the rate of recurrence. Our goal with this study was to implement pterygium surgery that was safe, easy to perform and with satisfactory recurrence rate. In the current study, patients with primary pterygium treated by one dose of 0.04%(0.4mg/ml) MMC applied for 3 minutes intraoperatively after BSR technique. In our study the recurrence rate was 4% through 1 year of follow up. We compare the results of our study with other studies in treatment of pterygium exision in different methods as shown in (Table 6).

In comparable to recurrence rates in studies with use BSR alone (Table 6) there was high recurrence rates which range between 40-88%, according to these studies the pterygium must not be excised without adjuvant.

In comparable to recurrence rates in studies with use of conjunctival autograft (CAG) as shown in (Table 6) which range between 2-39%, Kenyon et al. first described a CAG in 1985[99], from these studies in general the recurrence rate was less than BSR beside they were near or more than our result, and we prefer intraoperative MMC application than CAG and this coincide with study done by Vrabec et al. in 1993 & Chen et al. in 1998 in which the use of intraoperative MMC has the advantages of requiring less operation time and obviating the need for donor tissue and suturing and, thus, scarring at the donor site.[75], [76] In several randomized controlled trials, compared the recurrence rates of CAG with MMC by Akinci et al in 2007[77] and Sharma et al in 2000[78], the differences in recurrence rates were nonsignificant despite the superiority of CAG over MMC in preventing the pterygium recurrence. Young et al in 2004[79] in their study found recurrence rate higher in MMC than CAG while in the study done by Harpal Singh et al in 2009[80] it was apporximately equal in both groups and this augment our opinion in choice MMC as first line of treatment and leave the CAG for recurrence cases. In our study the average surgery time in the MMC was 20 minutes, half the average surgery time in the CAG (Kenyon et al. 1985). In a study done by Koranyi et al in 2012 the incidences of many complications were similar in both techniques.[81]

On the other hand, pterygium excision combined with CAG appears safe and effective, but was usually used only for recurrent lesions because CAG procedure is relatively more time consuming and skilful dissection of graft is required (Kenyon et al. 1985, Starck et al. 1991 & Allan et al. 1993) and this match our suggestion to use intraoperative MMC after BSR. Furthermore, in cases where the superior limbus is scarred (for example, glaucoma with trabeculectomy), an alternative site for harvest is required.[112] In conclusion, simple excision of pterygium followed by MMC or CAG both yielded acceptable results (Ma et al & Sharma et al in 2000).[57],[78]

In comparable to recurrence rates in studies with use of MMC 0.02-0.04% postoperatively as eye drops (Table 6) for a time range from 5-14 days the recurrence rate range between 0-37% which are much lower than BSR, but the recurrence rate nearly approach or higher than our result but with the risk of overuse from self-administration of this toxic chemotherapeutic agent by the patients themselves at home, and postoperative therapy entails repeated bathing of the entire ocular, nasolacrimal, and oropharyngeal surfaces for 5–14days with MMC, so we choice the intraoperative MMC for more savity as augmented by other studies.[61],[70],[83],[84] The use of high cumulative doses of MMC eye drops post-operatively, as well as poor selection of patients, can lead to the development of severe complications. To limit these complications, it is of utmost importance to set strict exclusion criteria, to use MMC only intra-operatively under controlled conditions, and to follow the patients closely until ocular surface re-epithelialization is complete.[49]

In comparable to recurrence rates in studies with intraoperative MMC range between 2-22% as shown in (Table 6) in which variable dosages of MMC (0.01-0.04%) for 0.5–5 minutes were applied, our result nearly match or less than these studies.[49],[85],[86],[87],[88] Single intraoperative application of MMC is comparatively safer as it localizes the effect on the tissue, do away problem of patient`s poor compliance and prevents dose dependent complications caused by inappropriate use.[89] MMC significantly reduces the rate of pterygium recurrence following its excision[82] by inhibiting the proliferation of fast growing cells, such as fibroblasts and vascular endothelial cells.[67] Intraoperative administration of MMC, represents an entirely different therapy from postoperative administration of MMC. With intraoperative administration of MMC, the surgeon has direct control over medication delivery, thus eliminating the risk of overuse from self-administration of this toxic chemotherapeutic agent by the patients themselves at home. MMC, used as eyedrops, is connected with serious complications such as glaucoma, corneal edema, corneal perforation, iritis and scleral thinning (Rubinfeld et al. 1994). When used as single application, MMC is less toxic. Studies of intraoperative MMC have reported minor side effects, such as low-grade ocular pain, photophobia, superficial punctate keratitis, and conjunctival granuloma[49],[86],[87],[88],[90],[91] these minor side effects match our results and we

identified no serious complication from the intraoperative use of MMC in any patient in our study.

Despite the excellent safety of intraoperative MMC, surgeons should ensure that intraoperative MMC therapy is not used in any patients with a condition that predisposes to poor wound healing, delayed epithelialization or patients with immune disorders, such as keratoconjunctivitis sicca, Sjo¨gren syndrome, meibomitis, blepharitis, dry eye, acne rosacea, atopic keratoconjunctivitis, or herpes keratitis, because of their propensity to develop serious eye complications with this medication.[92] Although intraoperative application of MMC appears to be highly efficacious in reducing the risk of pterygium recurrence, certain factors appear to contribute to higher risk of pterygium recurrence, even with this therapy. In our study patients treated with MMC, the mean age of those who developed a recurrence was (35 years), average age between (30-40years) was significantly lower than the patients who did not develop a recurrence in which mean age was (52.7 years), average age between (42-60years). These results match with studies done by Mastropasqua in 1996 and by Busin in 1986 that show younger age <50 years to be a significant risk factor for recurrence of pterygium after MMC.[76],[87],[93],[95] In contrast Tan et al in 1997[94] showed that the pterygium morphology, i.e., the fleshiness of the pterygium, rather than the age is the significant risk factor for pterygium recurrence which was not seen in our study. Chen et al in 1995 reported the mean time to recurrence from 3.7 to 4.8 months and only 6% were noted after the sixth postoperative month.[76] Pterygium recurrence was noted between 2–6 months postoperatively in two previous studies by Hayasaka in 1988 and Cano-Parra et al in 1995.[70],[86] This coincide with our result in which the mean time to recurrence is 4.5 months. In a study by Hirst et al in 1994[96] showed that nearly 50% of recurrences occurred within the first 3 month postoperatively and nearly all occurred within 1 year of pterygium removal. The findings in our study were similar: one recurrence (50%) was seen by the third postoperative month and the other(50%) in 6 months and all recurrences occurred within 12 months of surgery. These findings indicate that close patient follow-up during the first year after pterygium surgery is essential in evaluation of the final results of the treatment, and this match the study by Claus et al in 1998[97] and Lawrence in 1994 in which the follow-up time was 12 months for all patients is needed to identify a recurrent pterygium.

A recurrent pterygium often gives the patient more disability than the primary one; and is in addition more difficult to remove with a good result. It is therefore crucial to choose a surgical technique with a low recurrence rate. Many factors such as the type of pterygium, climatic characteristics, method of surgery and the experience of the surgeon may affect the recurrence rates after surgery. Every recurrence causes loss of conjunctival tissue, limitation of the movements of extraocular muscles, or formation of scar tissue besides the occurence of the same pathology. Therefore, the definitive therapy of pterygium by the primary surgery is extremely important.[98],[99],[100],[101]

Using MMC 0.01%-0.04% intraoperatively (for up to3- 5 minutes) and close control of the patients until the epithelisation of the ocular surface is complete, using these rules, in the past years we had no MMC related severe complications following pterygium surgery[57], except for some temporary postoperative minor side effects and this agument our choice in using the intraoperative topical MMC 0.04% for 3 minutes after BSR technique with good result regarding complications and recurrence.

A recurrent pterygium can be associated with decreased visual acuity due to involvement of visual axis and/or irregular astigmatism, extraocular motility restriction and symblepharon formation.[107]

In our follow-up of 12 months after the use of intraoperative MMC, we noted only early, minor side effects and complications like ocular discomfort, phtophobia, lacrimation, foreign body sensation, and ocular pain in 70% of our patients all resolve after 1 week.

Chemosis, oedema & hyperemia of surrounding conjunctiva occur in 60% of patient also resolve within 1 week. Corneal epithelial defect occurred in 4% of patients and resolve within 2 weeks. Granuloma occurred in 2% and treaed with topical steroid. Conjuctival avascularity occurred in 30% of patient & scleral avascularity occurred in 50% of patients.

We identified no serious complication from the intraoperative use of MMC in any patient in our study.

Our study was predominated by females over males. Female to male ratio was 2.125:1. In the study presented by Baig in 2008, this ratio was 3:1.[105] In a study done by Dr. Muhammad Rafiq et al. in 2013[108] male to female ratio was 4:1.

This result in our study may be due to females more blemish for cosmetic disfigurement than males beside the most females work in bread making so they subjected to direct flame.

The pterygium is twice as common in men as women in a studt by Akinci in 2007 and Ooldenburg in 1990.[109],[110] And this is not coincide with our result in which the pterygium is twice in women as men. The pterygium is uncommon before the age of 20 years. In our study the highest incidence has been reported in the age range of 41-60 years (70%), the lowest incidence has been reported in the age range of 21-40 (30%), this not match the results from study by Ooldenburg et al in 1990[110] in which the highest incidence has been reported in the age range of 20-40 years.

Patients presenting with primary pterygium were outdoor workers like drivers, labourers and farmers who were exposed to ultraviolet radiations, and indoor workers like, welders & backers who were exposed to flame, and this is the main reason that our study was predominated by females because in Iraq most house wifes made breads inside their houses by use gas or wood furances.

In our study the pterygium was common in outdoor workers (60%) and less in indoor workers (40%) and this match the results in studies done by Moran et al in 1984, Khoo et al in 1998, Coroneo et al in 1999, Luthra et al in 2001 & Ang et al in 2012.

The use of lubricants and sunglasses should be encouraged, especially in early pterygium and following excision, as this can decrease symptoms and possibly slow progression or recurrence.

In review of the literatures, we found that the wide variability of the postoperative outcome in these studies may reflect variations in patient demographics, definition of recurrence, study design, surgical technique, racial and environmental factors, and possibly others.

Table 6: Summary of findings of a meta-analysis studies.

Author	Year of Publica-tion	Technique	Number of Eyes	MMC Concentration%	MMC contact time (minutes)	Recurre- nce Rate(%)
Singh et al	1988	BSR	18			88
Lewallen	1989	BSR	16			40
Mahar & Nwokora	1993	BSR	15			60
Chen et al	1995	BSR	17			88
Lewallen	1989	CAG	17			17
Chen et al	1995	CAG	23			39
Manning et al	1997	CAG	18			22
Young et al	2004	CAG	52			2
Mahar et al	1993	PO MMC	17	0.04	qdsX2wks	0.0
Chen et al	1995	PO MMC	24	0.02	bdX5days	37
R Rachmiel et al	1995	PO MMC	38	0.02	bdX5days	2.6
Manning et al	1997	PO MMC	19	0.02	qdsX1wk	21
Banu M. et al	2000	PO MMC	34	0.02	qdsX5days	11.8
Atiya Rahman et al	2007	PO MMC	42	0.02	bdX2wks	20.5
Mastropasqua et al	1994	IO MMC	30	0.02	3	6.6
Frucht-Perry et al	1994	IO MMC	20	0.02	5	5
Cardillo et al	1995	IO MMC	45	0.02	3	6.6
Heiligenhaus et al	1995	IO MMC	18	0.02	5	22
Cano-Parra et al	1995	IO MMC	30	0.01	5	3.3
Hela et al	1996	IO MMC	87	0.01	3	5.75
Caliskan et al	1996	IO MMC	19	0.04	3	5.3
Mastropasqua et al	1996	IO MMC	45	0.02	3	12.5
Frucht-Perry et al	1996	IO MMC	49	0.02	5	4
Rubinfeld et al	1997	IO MMC	289	0.02	3	2.7
Manning et al	1997	IO MMC	19	0.04	3	10.5
Claus Pommerencke et al	1998	IO MMC	19	0.03	5	11
Panda et al	1998	IO MMC	25	0.02	3	12
Lam et al	1998	IO MMC	35	0.04	5	8.6
Banu Hosal et al	2000	IO MMC	38	0.02	5	5.3
Hon-Chun Cheng et al	2000	IO MMC	38	0.02	0.5	7.9
Al Young et al	2002	IO MMC	63	0.02	5	15.9
Imtiyaz Ahmad et al	2004	IO MMC	100	0.02	5	2
Young et al	2004	IO MMC	53	0.02	5	15.9
Atiya rahman et al	2007	IO MMC	42	0.02	3	10
Ashok K. Narsani et al	2008	IO MMC	31	0.02	5	16
Yesim Alltay et al	2012	IO MMC	20	0.02	5	15
Muhammad Rafiq et al	2013	IO MMC	50	0.02	5	16
Tommy C.Y. Chan et al	2015	IO MMC	39	0.02	5	15.4
Moustafa K. et al	2017	IO MMC	50	0.02	5	16
Present Study	2019	IO MMC	50	0.04	3	4

CONCLUSION

MMC administered intraoperatively 0.04% (0.4mg/ml) for 3 minutes is a safe and effective way to reduce the recurrence rate after BSR technique of pterygium. In the current study, the low pterygium recurrence rate (4%), the high level of cosmetic satisfaction, the simplicity of the procedure, the short surgery time average 20 minutes, and obviating the need for donor tissue and suturing, thus, scarring at the donor site, the minimal risk of minor side effects, and the lack of major complications after treatment lead us to recommend this regimen as the first choice for the treatment of primary pterygium.

Long term evaluation revealed that the use of MMC in pterygium surgery is safe, but for a strict selection of patients, controlled use of MMC and follow up for at least 1 year are required.

In our study we encountered no vision threatening complications resulting from MMC administered intraoperatively. As not any late onset recurrences appeared, we suggest that 12 month follow-up is satisfactory in future studies on pterygium surgery. For the treatment of recurrent pterygium, we recommend CAG as a more efficacious alternative.

So we prefer BSR technique followed by intraoperative MMC which was safe, simple and acceptable adjuvant for prevent recurrence, in comparism to MMC eye drops postoperatively in which the risk of overuse from self-administration of this toxic chemotherapeutic agent by the patients themselves at home, and postoperative therapy entails repeated bathing of the entire ocular, nasolacrimal, and oropharyngeal surfaces for 5–14days with MMC which carry high serious side effects and also prefer to another technique like CAG which is technically more difficult, time consume and inapplicable in cases with previous conjuctival disturbance.

Educational interventions to modify potential exposures like sun, dust, wind, flame ect., by use lubricants & wear protective sun glasses & hats especially in early pterygium and following excision, as this can decrease symptoms and possibly slow progression or recurrence & may assist in preventing pterygium.

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