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IP International Journal of Ocular Oncology and Oculoplasty

Journal homepage: www.innovativepublication.com

Original Research Article

Randomised controlled study of amniotic membrane graft versus conjunctival autograft in primary pterygium excision

Alhaj F Tasneem[1], Vittal I Nayak[1], Nischala Balakrishna[1,*], Krithika N[1], Singri Niharika Prasad[1], Nagalakshmi Narayanaswamy[1]

[1] *Dept. of Ophthalmology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India*

ARTICLE INFO

Article history:
Received 30-01-2020
Accepted 12-03-2020
Available online 24-04-2020

Keywords:
Pterygium excision
Amniotic membrane graft
Conjunctival autograft

ABSTRACT

Purpose: To study the outcome of amniotic membrane graft versus conjunctival autograft after primary pterygium excision surgeries amongst various genders and age groups and to compare recurrences, complications and pre and post-operative astigmatism in various grades of nasal and temporal pterygium.
Materials and Methods: A total of 90 eyes of 90 patients with previously unoperated primary pterygium were enrolled in a randomised control trial. The patients had a follow-up of 6 months during analysis and the results were compared retrospectively with patients who had pterygium excision surgeries with conjunctival autografts performed by the same surgeon.
Results: A higher proportion of males underwent grafting with amniotic membrane while more females underwent conjunctival autografting. The p value =0.011 was significant. A higher proportion of patients were between the ages of 31-40 years and the p value=0.001 was significant. A majority of patients from both groups had nasal pterygium with p value=0.026 being significant. The overall astigmatism pre operatively from both groups=0.431 and 0.143 postoperatively.
Conclusion: Amniotic membrane grafting in primary pterygium surgery led to fewer complications, recurrences and astigmatism postoperatively and was more useful in patients who may have lesser amounts of conjunctiva for future surgeries.

1. Introduction

Pterygium is a wing-shaped, triangular fibrovascular growth that extends from the conjunctiva onto the nasal, temporal or both aspects of the cornea.[1] It maybe atrophic, stationary or progressive and is commonly seen in tropical and subtropical areas. Pterygium can impair vision by altering the tear film, inducing astigmatism, photophobia, increased watering from the eyes and diplopia due to contraction of Tenon's capsule. Surgery is currently the only known treatment for pterygium.[2]

The various surgical techniques differ in the method of excision and approach to the bare area created.[3–7] The defect area is left exposed without any graft after excision in the bare sclera method[8,9] or it is covered by the conjunctiva surrounding it as in primary closure method.[10,11] or it is covered with a pedicle flap[12] or transposition of head of pterygium. Defects can also be covered by a conjunctival autograft.[12–22] Rarely, tissues sources like buccal mucosa membrane grafts, lamellar keratoplasty.[23,24] penetrating keratoplasty[6] or sclerokeratoplasty[25,26] can also be used. Other techniques are yttrium-aluminium-garnet laser treatment[27] and the polishing technique by Barraquer.[28]

Owing to the high rates of recurrence amongst post-operative pterygium cases, newer techniques like cut-and-paste technique[29] with fibrin glue and use of adjunctive treatments like Thiotepa,[6,30,31] Mitomycin C,[32–37] 5-Fluorouracil,[38] Ciclosporin A[39] or Daunorubicin[40] have proved effective and have also helped reduce the postoperative pain and shorten the surgical time. Nevertheless, these methods are associated with poor epithelial

* *Corresponding author*.
E-mail address: nischalabalakrishna@gmail.com (N. Balakrishna).

https://doi.org/10.18231/j.ijooo.2020.007

healing,[34] superficial punctate keratitis,[35] scleral thinning and ulceration, infections, increased intraocular pressure and endophthalmitis.[41,42]

Taking into consideration the above aspects, Conjunctival autografting has proved to be the safest and more practical technique. Although they help prevent the recurrence of pterygium, they carry the risk of compromising the outcome of a probable glaucoma filtering surgery in the future. Moreover, Pterygium with large conjunctival involvement or those with more than one head may require larger amounts of healthy conjunctiva from the same or opposite eye.

The preserved human amniotic membrane grafts are an alternative to these conjunctival autografts. They not only help in retaining the healthy conjunctival tissue but also helps in decreasing the tissue handling, intraoperative time, less raw area for healing and in preventing recurrences[43–49] by inhibition of inflammation by restricting chemokine expression by fibroblasts[50,51] and expression of interleukin1 by the epithelial cells and restriction of neovascularisation by inhibiting vascular endothelial cell growth.[52] The amniotic membrane graft is also been used increasingly in the treatment of other ocular surface disorders,[53] including corneal surface epithelial defects with ulceration,[54] to help in reconstructing ocular surfaces in malignancies of conjunctiva or even after chemical or thermal burns which leads to scarring,[55,56] ocular cicatricial pemphigoid and in syndromes like Stevens-Johnson syndrome,[57] it helps to decrease corneal scarring after the use of excimer laser photoablation,[58] to prevent the adhesion and in the repair of leaking blebs after a trabeculectomy surgery[59] and to help reconstruct defects in the conjunctiva after pterygium excision.[60]

2. Materials and Methods

2.1. Patients

The study was carried out for a period of one year from October 2018- September 2019 in 90 eyes of patients with primary pterygium. These patients who met the inclusion criteria of the study were enrolled prospectively and in order to be enrolled, all the patients had been questioned and the patient details were reviewed to exclude those having any major systemic diseases such as diabetes mellitus or collagen vascular disease. An extensive ophthalmic examinations including visual acuity, intraocular pressure using applanation tonometry, slit lamp examinations, posterior segment and fundus examinations and tests to evaluate for dry eyes like Schirmer's test and the tear film break up time and epithelial fluorescein staining were performed to make sure that none of the patients had any serious eye diseases such as dry eye, cicatricial pemphigoid, glaucoma or vitreoretinal disease. All cases in the amniotic membrane graft group showed that the size of the pterygium was at least 2mm into the cornea (Grade 2 pterygium) (Figure 4). All patients had a minimum follow-up of 6 months. The results were compared retrospectively with those patients who underwent pterygium excision surgeries with conjunctival autografts with autologous serum during the same study period and those which were operated by the same surgeon. The final appearance of the pterygium was graded based on a criterion given by Prabhasawat et al.[61] Grade 1 indicates no difference between the operated area from a normal area. Grade 2 indicates the presence of some fine episcleral vessels in the excised area which were encroaching up to the limbus. Grade 3 indicates that in addition to Grade 2 there was fibrous tissue in the area of excision which was not invading onto the cornea whereas Grade 4 showed its invasion onto the cornea suggesting true recurrence.

2.2. Inclusion criteria

1. Patients diagnosed with primary pterygium at Vydehi Institute of Medical Sciences and Research Centre, Bangalore and those who met the indications for surgical treatment.
2. Patients with pterygium who agreed to sign the informed consent to enrol into the study

2.3. Exclusion criteria

1. Patients having glaucoma in the opposite eye
2. Patients with intraocular pressure more than 21mmHg in the affected eye
3. Patients who underwent previous glaucoma filtration procedures like trabeculectomy, patients with pemphigoid and other dermatological and lid conditions.

2.4. Surgical procedure

2.5. Amniotic membrane preparation

The preparation and preservation of the human amniotic membrane is in conjunction with Kim and Tseng method.[62] These human placentas are acquired after elective caesarean section surgeries once thorough serology testing is completed and washed with 0.9% normal saline and Earl's balanced salt solution which contains 50mg/ml penicillin, 100 mg/ml neomycin,50mg/ml streptomycin and 2.5mg/ml amphotericin B to remove all the blood clots and contamination. The separated amniotic membrane is then flattened onto nitrocellulose papers with epithelium facing up. The membrane is then cut into pieces and put into tubes containing 1:1 mixture of Dulbecco's modified Eagle's Medium and glycerol. This was then preserved in at -70 degree Celsius until further use. At the time of use, this membrane was thawed and was soaked in normal saline mixed with Gentamycin(3mg/ml) for about 3 minutes. During our study period a total of 5 amniotic

membranes were used.

2.6. Pterygium excision

Before the surgery, hand written informed consents for the procedure was obtained from every patient. All surgeries were performed by the same surgeon to ensure uniformity in techniques. Peribulbar anaesthesia with 2% Lignocaine containing 5IU per ml of hyaluronidase and 0.5% Bupivacaine was used in all patients. For nasal pterygium, the head of pterygium was separated at the limbus by passing an iris repositor and dissected with the help of a toothed forceps. After excising the head and most of the body of the pterygium, subconjunctival Tenon's tissue was separated from the overlying conjunctiva and excised. Precautions were taken to prevent damage to the medial rectus muscle. The conjunctiva above and below the pterygium was trimmed to create a rectangular area of bare sclera. Residual fibrovascular tissue over the cornea was excised either by toothed forceps or by gently scarping with a Tooke's forceps. The fully dissected body of pterygium was cauterized with a bipolar wet field cautery in a linear fashion and cut at the cautery points so that there was no bleeding. The sclera was not with cautery at any point of time.

2.7. Amniotic membrane graft

Rectangular conjunctival defects ranging from approximately 5*7 to 6*8 mm or even larger were created. This bare sclera area was covered with amniotic membrane, which was oriented in such a way that the basement membrane side faced upwards. The preserved amniotic membrane graft was then cut 1-2 centimetres larger than the defect and was placed on the defect and kept in situ for 10 minutes till autologous serum held the graft in position. Sterile cellulose spear headed sponges were used to remove excess fluid percolating beneath the graft in order to facilitate faster sticking of graft to the bare area(Figure 5)

2.8. Postoperative followup

Postoperatively, the patient was started on oral serratio peptidase tablets 2 times per day for five days after food, antacid tablets once a day before food. Topical antibiotic with steroid drops were used 6 times per day for one week and then tapered weekly thereafter. Nepafenac drops were used three times per day for one month. Lubricating drops (0.5% carboxymethylcellulose) were used four times a day. Patients were followed monthly from the first month, then bimonthly from fourth month to 1 year and thereafter, regular follow ups at 3 months intervals. Photographs were taken preoperatively and postoperatively after one month. Complications were noted if any. Recurrence were defined as any fibrovascular growth beyond the limbus onto the cornea, and was assessed and confirmed by another observer by slit lamp examination or by postoperative photographs.

3. Statistical Analysis

All demographic data including gender, age, grade, nasal or temporal pterygium were compared between conjunctival autografts and amniotic membrane grafts using x^2 test. The recurrences, complications and astigmatism pre and postoperatively at 6 months were also analysed using the x^2 test.

4. Results

The gender distribution of patients studied, as shown in Table 1, shows that 50 subjects were males (55.6%) out of which 19(42.2%) underwent pterygium excision with conjunctival autograft and 31(68.9%) underwent pterygium excision with amniotic membrane graft. The p value= 0.001 which was statistically significant. Table 2, shows the age distribution of the patients. 14(15.6%) were between 20-30 years of age, 5(11.1%) underwent pterygium excision with conjunctival autograft and 9(20%) underwent pterygium excision with conjunctival autograft. A total of 37(41.1%) were between 31-40 years of age and 13(28.9%) underwent pterygium excision with conjunctival autograft and 24(53.3%) underwent pterygium excision with amniotic membrane graft. A total of 16(17.8%) were between 41-50 years and 9(20%) underwent pterygium excision with conjunctival autograft and 7(15.6%) underwent pterygium excision with amniotic membrane grafting. A total of 14(15.6%) were between 51-60 years and 11(24.4%) belonged to the conjunctival autograft group while 3(6.7%) belonged to the amniotic membrane graft group. A total of 5(5.6%) belonged to the age groups between 61-70 and 5(11.1%) underwent conjunctival autografting while no one underwent amniotic membrane grafting. There was a total of 4(4.4%) subjects more than 70 years of age out of which 2(4.4%) belonged to the conjunctival autograft group and 2(4.4%) belonged to the amniotic membrane group. A total of 45(100%) in each category, that is, pterygium excision with conjunctival autograft and pterygium excision with amniotic membrane grafting were studied. The mean+/- SD showed a total of 42.21+/-12.93, 46.53+/-13.51 belonging to the conjunctival autograft group and 37.89+/-10.85 belonging to the amniotic membrane group. The p value=0.001 which was statistically significant. Table 3 compares the total number of patients with nasal and temporal pterygiums amongst the two classes. A total of 84(93.3%) had nasal pterygiums out of which 45(100%) underwent pterygium excision with conjunctival autograft and 39(86.7%) underwent pterygium excision with amniotic membrane grafting. A total of 6(6.7%) had temporal pterygiums and out of these none underwent pterygium excision with conjunctival autografting but 6(13.3%) underwent pterygium excision with amniotic membrane

grafting. The p value=0.026 which was statistically significant. Table 4 and Table 5 show the pre-operative and postoperative astigmatism in both the groups. The preoperative astigmatism in the conjunctival autograft group was -0.49+/-0.63 and in the amniotic membrane graft group was -0.59+/-0.49. The total astigmatism was -0.54+/-0.56 and the p value=0.431 which is statically significant. In the postoperative period the astigmatism in the conjunctival autograft group was -0.53+/-0.52 and in the amniotic membrane group was-0.17+/-1.59 and the total astigmatism was -0.35+/-1.19 and the p value=0.143 which is statically significant. Table 6 shows the various grades of pterygiums and compares them in both the groups. There were no grade 1 pterygiums in both the groups. The total number of grade 2 pterygiums was 44(48.9%). The conjunctival autograft had 14(31.1%) and the amniotic membrane group had 30(66.7%). The total number of grade 3 pterygiums were 41(45.6%) with 28(62.2%) in the conjunctival autograft group and 13(28.9%) in the amniotic membrane group. The total number of grade 4 pterygiums 5(5.6%) with 3(6.7%) in the conjunctival autograft group and 2(4.4%) in the amniotic membrane group. Table 7 shows the complications postoperatively in both the groups. Graphs 1 and 2 shows the same. A total of 74(82.2%) had no complications with 36(80%) belonging to the conjunctival autograft group and 38(84.4%) belonging to the amniotic membrane group. 3(3.3%) cases had graft shrinkage with none seen in the conjunctival autograft group and 3(6.7%0 seen in the amniotic membrane group. A total of 6(6.7%) cases had subconjunctival haemorrhage with 5(11.1%) seen in the conjunctival autograft group and 1(2.2%) seen in the amniotic graft group. A total of 3(3.3%0 cases had Ocular surface squamous neoplasia, with 1(2.2%) seen in the conjunctival autograft group and 2(4.4%) seen in the amniotic membrane group.1(1.1%0 case had an epithelial inclusion cyst and was seen in the amniotic membrane graft group with no such cases seen in the conjunctival autograft group.3(3.3%) cases had scleral ischaemia with scleritis with 3(6.7%) belonging to the conjunctival autograft group and none seen in the amniotic membrane graft group. Table 8 and graph 3 compares the recurrence of pterygium in both the groups. There were no recurrences in 82(91.1%) cases with 37(82.2%) belonging to the conjunctival autograft group and 45(100%) belonging to the amniotic membrane graft group. There were 8(8.9%) recurrences and all were seen in the conjunctival autograft group 8(17.8%). The p value=0.006 which was significant.

5. Discussion

The excess proliferation of subconjunctival fibroblasts and vessels which are activated due to inflammation post-surgery or trauma and overexpression of matrix metalloproteins are responsible for the pterygium recurrences.[63–66]

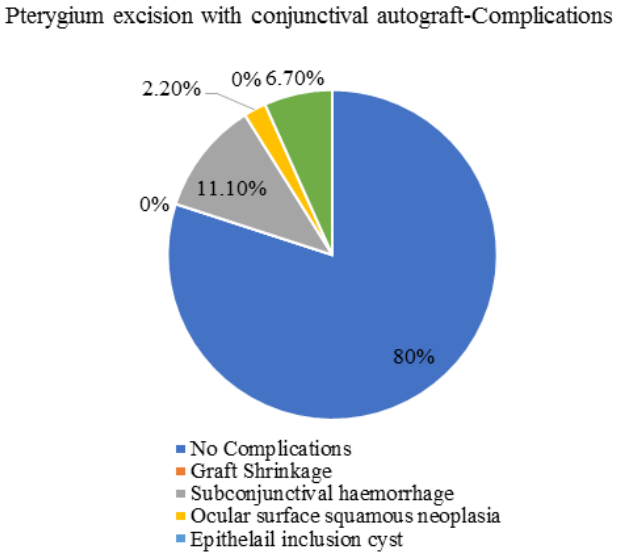

Fig. 1: Showing complications afterpterygium excision with conjunctival autograft

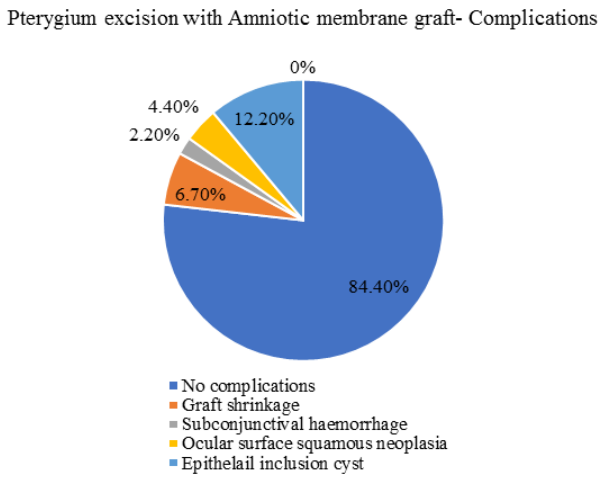

Fig. 2: Showing complications afterpterygium excision with amniotic membrane grafting

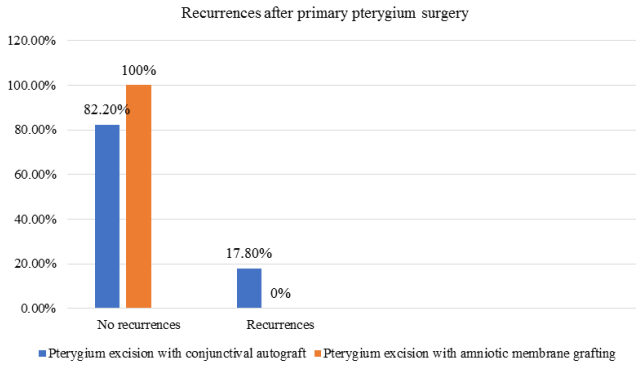

Fig. 3: Showing the recurrence rates ofpterygium after conjunctival auto grafting versus amniotic membrane grafting

Table 1: Gender distribution of patients studied

Gender	Pterygium excision with conjunctival autograft	Pterygium excision with amniotic membrane graft	Total
Male	19(42.2%)	31(68.9%)	50(55.6%)
Female	26(57.8%)	14(31.1%)	40(44.4%)
Total	45(100%)	45(100%)	90(100%)

P=0.011

Table 2: Age distribution of patients studied

Age in years	Pterygium excision with conjunctival autograft	Pterygium excision with Amniotic membrane graft	Total
20-30	5(11.1%)	9(20%)	14(15.6%)
31-40	13(28.9%)	24(53.3%)	37(41.1%)
41-50	9(20%)	7(15.6%)	16(17.8%)
51-60	11(24.4%)	3(6.7%)	14(15.6%)
61-70	5(11.1%)	0(0%)	5(5.6%)
>70	2(4.4%)	2(4.4%)	4(4.4%)
Total	45(100%)	45(100%)	90(100%)
Mean+/-SD	46.53+/-13.51	37.89+/-10.85	42.21+/-12.93

P=0.001**

Table 3: Nasal /Temporalpterygium

Nasal/Temporal pterygium	Pterygium excision with conjunctival autograft	Pterygium excision with amniotic membrane graft	Total
Nasal pterygium	45(100%)	39(86.7%)	84(93.3%)
Temporal pterygium	0(0%)	6(13.3%)	6(6.7%)
Total	45(100%)	45(100%)	90(100%)

P=0.026

Table 4: Astigmatism

Astigmatism	Preop	Postop	%difference
Pterygium excision with conjunctival autograft(n=45)			
<-0.25	26(57.8%)	23(51.1%)	-6.7%
-0.25 to 0	9(20%)	14(31.1%)	11.1%
0	8(17.8%)	6(13.3%)	-4.5%
0-0.25	0(0%)	2(4.4%)	4.4%
>0.25	2(4.4%)	0(0%)	-4.4%
Pterygium excision with amniotic membrane graft (n=45)			
<-0.25	28(62.2%)	22(48.9%)	-13.3%
-0.25 to 0	10(22.2%)	12(26.7%)	4.5%
0	7(15.6%)	10(22.2%)	6.6%
0-0.25	0(0%)	0(0%)	0.0%
>0.25	0(0%)	1(2.2%)	2.2%

Table 5: Astigmatism

Astigmatism	Pterygium excision with conjunctival autograft	Pterygium excision with amniotic membrane autograft	Total	P value
Pre op	-0.49+/-0.63	-0.59+/-0.49	-0.54+/-0.56	0.431
Post op	-0.53+/-0.52	-0.17+/-1.59	-0.35+/-1.19	0.143

Table 6: Grade

Grade	Pterygium excision with conjunctival autograft	Pterygium excision with amniotic membrane graft	Total
Grade 1	0(0%)	0(0%)	0(0%)
Grade 2	14(31.1%)	30(66.7%)	44(48.9%)
Grade 3	28(62.2%)	13(28.9%)	41(45.6%)
Grade 4	3(6.7%)	2(4.4%)	5(5.6%)
Total	45(100%)	45(100%)	90(100%)

Table 7: Complications

Complications	Pterygium excision with conjunctival autograft	Conjunctival excision with amniotic membrane graft	Total
No complications	36(80%)	38(84.4%)	74(82.2%)
Graft shrinkage	0(0%)	3(6.7%)	3(3.3%)
Subconjunctival haemorrhage	5(11.1%)	1(2.2%)	6(6.7%)
Ocular surface squamous neoplasia	1(2.2%)	2(4.4%)	3(3.3%)
Epithelial inclusion cyst	0(0%)	1(2.2%)	1(1.1%)
Scleral ischaemia with scleritis	3(6.7%)	0(0%)	3(3.3%)
Total	45(100%)	45(100%)	90(100%)

Table 8: Recurrence

Recurrence	Pterygium excision with conjunctival autograft	Pterygium excision with amniotic membrane graft	Total
No recurrence	37(82.2%)	45(100%)	82(9.1%)
Recurrence	8(17.8%)	0(0%)	8(8.9%)
Total	45(100%)	45(100%)	90(100%)

P=0.006**

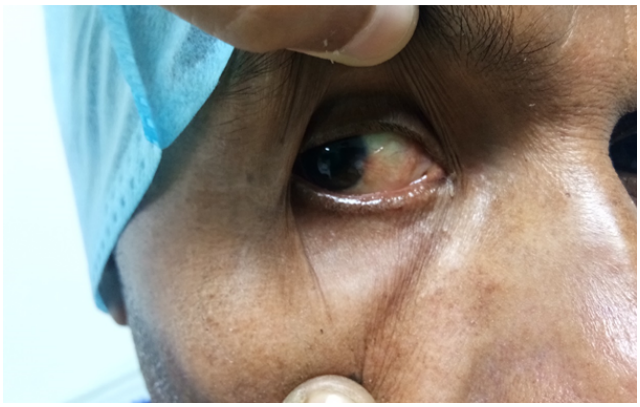

Fig. 4: Pre- operative picture of a patient with a grade 2 nasal pterygium who underwent pterygium excision with an amniotic membrane graft

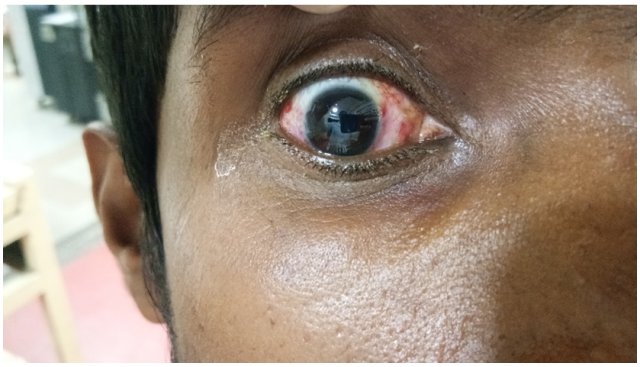

Fig. 5: The post-operative picture of the same patient one week after undergoing pterygium excision with amniotic membrane grafting

Amniotic membrane contains various matrix proteins[67] facilitating adhesion,[68,69] migration,[70] differentiation[71,72] and inhibition of apoptosis of epithelial cells.[73,74] The amniotic membrane is capable of binding growth factors which help in wound healing.[75–78]

Factors present in the amniotic membrane may change after preservation wherein it supresses the expression of transforming growth factor beta 1, 2, 3, receptor type 2 and myofibroblast differentiation in the corneal and the limbal fibroblasts and also opposes signalling pathway of transforming growth factor beta, CD-44, Beta 1 integrin and FGFR1/flg of the pterygium fibroblasts.[79]

The amniotic membrane matrix prevents extracellular matrix formation by these fibroblasts promoting conjunctival epithelial wound healing and decreasing recurrences. It also helps in the prevention of inflammation by inhibiting chemokines expression by the fibroblasts and interleukin 1 expression by epithelial cells and inhibits

new vessel formation by inhibiting vascular endothelial growth, presence of anti-angiogenic or anti-inflammatory proteins and protease inhibitors.[80] Tissue inhibitors of metalloproteinases are remarkable in amniotic membrane preservation following cryopreservation.[81]

6. Conclusion

The amniotic membrane contains a very thick basement membrane and a vascular matrix which are responsible in facilitating the migration of epithelial cells and promoting epithelial differentiation and in preventing epithelial apoptosis. These factors are responsible for the amniotic membrane to permit rapid epithelialisation. The amniotic membrane grafts have less surgical manipulation which decrease postoperative reaction in the eye and cause no graft shrinkage. There is also better adhesion and less oedema formation. These are commercially available and are very economical to patients especially those belonging to the lower socio-economic status. From this study, we observed that more male patients underwent pterygium excision with amniotic membrane autograft as opposed to female patients who underwent conjunctival autograft after primary pterygium excision. All patients who underwent pterygium excision with conjunctival autograft had nasal pterygiums while majority of the patients who underwent pterygium excision with amniotic membrane autograft had nasal pterygiums while a few had temporal pterygiums as well. More astigmatism was noticed after pterygium excision with conjunctival autograft as compared to pterygium excision with amniotic membrane autograft. Most of the cases from both the study groups had grade 2-3 pterygiums with few grades 4 pterygiums with no grade 1 pterygiums. Fewer complications and no recurrences were noticed in the pterygium excision with amniotic membrane graft study group which was in contrast to the pterygium excision with conjunctival autograft group which saw complications as well as recurrences.

Although this study shows that conjunctival autografts are less efficient than amniotic membrane grafts in reducing recurrences, complications and astigmatism after primary pterygium excision, it also indicates that this technique can be used as an alternative in the surgical management of the condition, especially when techniques like the bare sclera method has such high recurrence rates. Amniotic membrane grafts should nevertheless be considered as the first choice especially in advanced cases with diffuse conjunctival involvement where one might like to preserve donor bulbar conjunctiva for a prospective glaucoma filtering procedure or any other ocular procedure in the future.

7. Source of funding

None.

8. Conflict of interest

None.

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Author biography

Alhaj F Tasneem Professor

Vittal I Nayak Professor and HOD

Nischala Balakrishna Junior Resident

Krithika N Junior Resident

Singri Niharika Prasad Junior Resident

Nagalakshmi Narayanaswamy Junior Resident

Cite this article: Tasneem AF, Nayak VI, Balakrishna N, Krithika N , Prasad SN, Narayanaswamy N. **Randomised controlled study of amniotic membrane graft versus conjunctival autograft in primary pterygium excision**. *IP Int J Ocul Oncol Oculoplasty* 2020;6(1):33-41.