Efficacy of Ipsilateral, Focal-Simple Limbal Epithelial Transplantation for Large Primary Nasal Pterygia Treatment

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Abstract: *Purpose:* The long-term success of pterygium surgery is subject to treatment of the limbal stem cell defect. The purpose of this study is to present an alternative method to conjunctival autografting in patients with large pterygia and consequently a large limbal stem cell defect.

Methods: 38 Patients with primary nasal pterygium of more than 5 mm limbal involvement were selected for the procedure. Simple limbal epithelial transplantation with human amniotic membrane graft placement over the bare sclera after pterygium excision was done. Patients were followed-up for a period of 12 months.

Results: From post-operative day 7, patients had significant improvement in complaints and ocular surface morphology. We reported only one case of graft failure which was a consequence of patient's non-compliance with post-operative medications and follow-up.

Conclusion: Focal-simple limbal epithelial transplantation is an effective alternative to conjunctival limbal autografting in patients with large pterygia where preservation of virgin conjunctiva is prudent for future ocular surgeries.

Keywords: Pterygium, Limbal stem cell deficiency, Human amniotic membrane, Conjunctival autografting, Simple limbal epithelial transplantation.

INTRODUCTION

Pterygium is an ocular surface disorder characterized by a wing-shaped proliferative subepithelial ingrowth [1, 2]. The extension of pterygium onto the limbus and its consequent invasion of the cornea is attributed to a secondary limbal stem cell deficiency (LSCD) caused by a biochemical cascade initiated by damage from ultraviolet radiation [3, 4]. The prevalence of pterygium in adults in central India is around 8% [5]. Patients present with cosmetic problems, ocular discomfort, and visual disturbance [6]. Throughout history, dating as far back as 1000 B.C., many surgical and medical treatment modalities have been employed to remove the pterygium tissue [7]. In the past three decades, considerable surgical success has been achieved after the recognition of the role of stem cells in the pathogenesis of this disorder but no surgical technique entirely prevents recurrence [8]. The conventional gold standard/ primary treatment has been conjunctival limbal autografting (CLAu) as described by Kenyon [9]. But as large pterygia leave an even larger area of bare sclera after excision, it is not prudent to use nascent conjunctiva to cover the large defect as it damages the healthy ocular surface. It also potentially leads to a higher chance of recurrence of the excised pterygium due to the associated large LSCD in cases requiring larger graft [10]. A novel technique known as simple limbal epithelial transplantation (SLET) was reported by Sangwan *et al* in 2012 to treat the LSCD, in ocular burn patients, where healthy limbal tissue in the form of small lenticules of stem cells was grafted along with an amniotic membrane over the recipient cornea and bare sclera [11]. A modification to the technique of Sangwan *et al* but employing the same principles was described by Bogantes *et al.* to provide replacement of conjunctiva and limbal stem cells in pterygium excision, thus preserving virgin conjunctiva [12].

As the main deterrent to the CLAu technique is the large size of the pterygium tissue, we undertook a study to analyze the efficacy of modified SLET technique wherein autologous ipsilateral focal limbal stem cell transplantation along with human amniotic membrane (hAM) transplantation was performed in large primary nasal pterygia to preserve virgin conjunctiva and to replace the lost limbal stem cells.

MATERIALS AND METHODS

We conducted a prospective interventional study "Focal ipsilateral simple limbal epithelial transplantation (Focal-SLET) for large primary nasal pterygia treatment" to assess the outcome of focal SLET with

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amniotic membrane grafting. The study was conducted on 38 eyes of 38 patients presenting to our out-patient department with large, primary nasal pterygium where the height of limbal involvement exceeded 5 mm. The study was approved by the institutional review board and ethics committee as per Reg. No. ECR/748/Inst/MP2015 and IEC No. SAIMS/IEC/2019/46. A written informed consent was obtained from all participants and the study was conducted as per the principles laid out in the Declaration of Helsinki [13].

Inclusion Criteria

1. Patients presenting with ≥Grade 2 primary nasal pterygium (Figure **1** and **2**) [14].
2. Pterygium width of 5 mm or more at limbus
3. No association with any other ocular surface disorder
4. Patient consenting for study and at least 12 months follow-up

Figure 1: Clinical grading of pterygium (Figure 2).

Grade	Extent of Pterygium
Grade 1	Pterygium tissue just reaching the limbus
Grade 2	Pterygium tissue between limbus and pupillary border
Grade 3	Pterygium tissue reaching the pupillary border
Grade 4	Pterygium tissue crossing the pupillary border

Exclusion Criteria

1. Patients presenting with recurrent pterygium
2. Associated ocular surface disorder
3. Previous history of ocular surgery
4. History of hypersensitivity reaction to blood components

Surgical technique (Figure **3**):

After instillation of 0.5% proparacaine topically, a lid speculum was placed to achieve adequate exposure to the surgical field. The size of pterygium tissue at its maximum width at canthus and the limbus, and the corneal encroachment was measured with a pair of calipers. A subconjunctival block with 2% lidocaine was given below the pterygium tissue. The conjunctiva overlying the pterygium was cut 1 mm away and

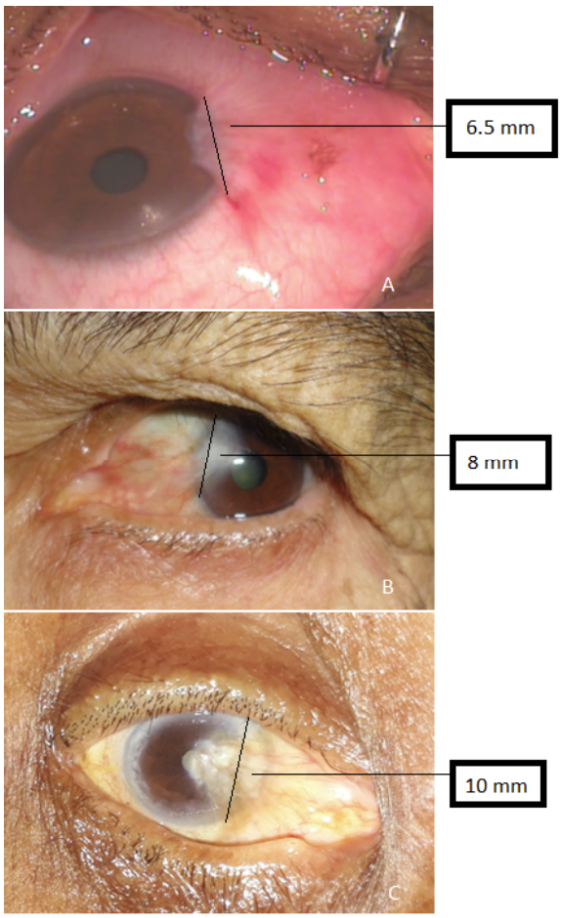

Figure 2: Grading of pterygium with limbal involvement: A- Grade 2; B- Grade 3; C- Grade 4. The black solid line shows limbal involvement.

parallel to the limbus covering the whole width of the pterygium. The pterygium tissue was undermined along its entire length till the medial canthus and the subconjunctival adhesions were removed. The pterygium tissue was exposed. The pterygium along with the underlying Tenon's was cut with the tenotomy scissors starting from the canthus. Then the pterygium was excised from the body at the canthus, reflected over the cornea and peeled off by reverse peeling technique, holding at limbus and moving towards centre. The remnants of pterygium tissue over the cornea were removed with a #15 blade by smooth keratectomy. The area of bare sclera was measured with a pair of calipers. A human amniotic membrane graft of size 1 mm larger than the size of the bare sclera was placed over it. The graft was secured in place by fibrin glue and by tucking the edges under the nascent conjunctival margins. A #15 blade was used to create a 2x2 mm strip of healthy limbal epithelial stem cell tissue from the supero-temporal quadrant of the same eye as the excised pterygium. This tissue was then cut into multiple pieces with Vannas scissors and

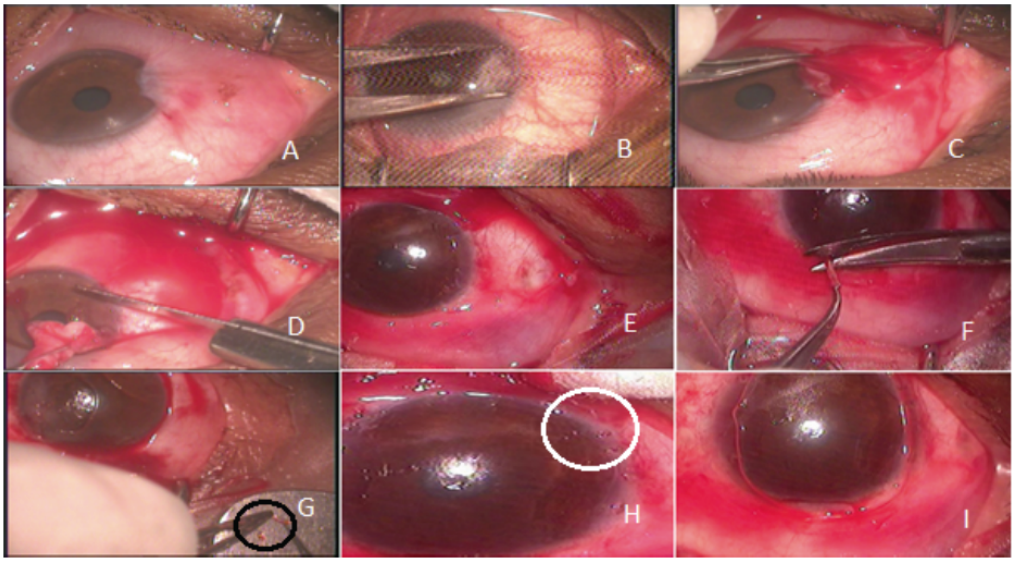

Figure 3: Surgical Steps: A- Pterygium tissue; B- Measurement of limbal involvement by calipers; C, D- Excision of pterygium by reverse peeling technique; E- Placement of amniotic membrane over bare sclera; F- Ipsilateral healthy limbal stem cell harvesting; G- Limbal stem cell fragmentation (in black solid circle); H- Placement of limbal stem cells over amniotic membrane (in white solid circle); J- Placememt of soft bandage contact lens.

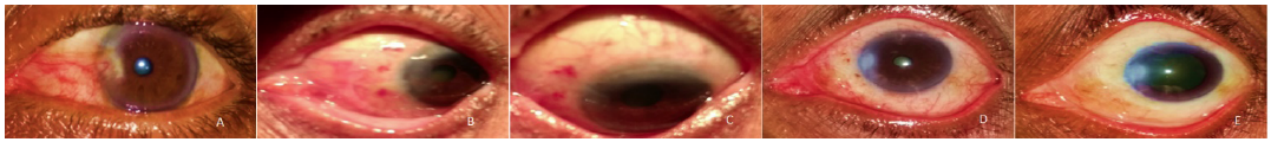

Figure 4: A- Pre-operative pterygium growth; B- Post-operative day 1; C- Post-operative day 7 showing limbal harvest site; D- Post-operative day 14; E- Post-operative day 30.

placed on the limbus over the amniotic membrane graft with fibrin glue. Then the corneal surface was covered with a soft bandage contact lens (BCL) and the eye was patched. The eye patch was kept overnight. From post-operative day (PoD) 1, patients were started on topical moxifloxacin 0.5%, prednisolone 1%, and carboxymethylcellulose 0.5% every 4 hours. All patients were followed-up on days 7, 15, 30, and 45 and then 3 monthly up to a period of 12 months (Figure **4**).

The soft BCL was removed on PoD 7. The topical corticosteroid was tapered over a period of 1 month. The donor site was observed on the follow-up visits for any signs of stem cell deficiency like limbal ischemia and neovascularization; and for signs of adequate healing. The graft site was observed for signs of recurrence as well as signs of any post-operative complications.

OBSERVATIONS

It was observed that more than half the number of enrolled patients were female (Figure **5**).

Figure 5: Observation of gender distribution.

Number of Patients	Gender	
	Male	Female
26	10	16
10	02	08
02	00	02
38	**12 (31.57%)**	**26 (68.42%)**

Most patients presented with a grade 2 nasal pterygium. Most common age group of presentation was 46-60 years while only five patients presented in the seventh decade or later (Figure **6**).

Most patients had a large limbal involvement of >8 mm (36.8%). 26% of the participants had limbal width of nasal pterygium less than <6 mm (Figure **7**).

Cosmetic concerns and foreign body sensation were the main causes of presentation (Figure **8**). A total 55.26% patients underwent surgery primarily due to cosmetic concerns from the pterygium (Figure **9**).

Figure 6: Relationship between age group and grade of pterygium.

Age Group (years)	Grade of Pterygium			Total
	Grade 2	Grade 3	Grade 4	
30-45	07	03	01	**11 (28.94%)**
46-60	16	05	01	**22 (57.89%)**
>60	03	02	00	**05 (13.15%)**
Total	**26**	**10**	**02**	

Figure 7: Relationship between size of pterygium at limbus and grade of pterygium.

Width at limbus	Grade of Pterygium			Total
	Grade 2	Grade 3	Grade 4	
5-5.9 mm	07	02	01	**10 (26.3%)**
6-6.9 mm	01	02	01	**04 (10.5%)**
7-7.9 mm	06	04	00	**10 (26.3%)**
>8 mm	12	02	00	**14 (36.8%)**

Figure 8: Relative frequency of presenting complaints.

Complaint	Number of patients (Percentage)
Cosmesis	32 (84.21%)
Foreign body sensation	26 (68.42%)
Redness	20 (52.63%)
Watering	16 (42.10%)
Visual impairment	08 (21.05%)

Figure 9: Indications for surgery.

Complaint	Number of patients (Percentage)
Cosmetic concern	21 (55.26%)
Foreign body sensation	09 (23.68%)
Watering	06 (15.78%)
Diminution of vision	02 (05.26%)

Figure 10: Post-operative complaints of patients after surgery.

Post-operative complaints	PoD* 1	PoD 7	PoD 15	PoD 30	PoD 45
Watering	14	06	03	01	01
Cosmesis	11	04	03	01	00
Pain	09	00	00	00	00
FB sensation	08	03	03	03	01
Redness	08	04	04	02	01
Visual Impairment	04	02	02	01	00

*PoD: Post-operative day

All the participants had complaints of localized pain, foreign body sensation and watering on first post-operative day. Complaints of foreign body sensation and watering persisted in more than half of the patients until day 7. By post-operative day 15, a significant number of patients reported relief in their symptoms (Figure **10**).

On day 01, amniotic membrane edema was found in four patients all of whom were managed by

Figure 11: Management of post-operative complications.

Post-operative complications	Number of patients	Symptoms/Signs at presentation	Intervention/Management	Recovery period after intervention
Amniotic membrane edema	04	Chemosis	Increased frequency of corticosteroid at presentation on PoD* 1	10-14 days
Displacement of Bandage contact lens	03	Redness, foreign body sensation	Replacement of Bandage contact lens at presentation on PoD 7	Immediate
Sub-amniotic membrane hemorrhage	02	Red eye	Vitamin C at presentation on PoD 1	21 days
Displacement of amniotic membrane graft	02	Mild retraction without exposure of bare sclera	Increased frequency of lubricant on presentation at PoD 7	14-28 days
Early signs of recurrence	02	Inflammatory fibrovascular tissue	Presentation at PoD 21- increased frequency of corticosteroid	50 days
Granuloma	01	Redness, foreign body sensation	Presentation on PoD 15- increased frequency of CS	30 days
Loss of stem cell lenticules	01	Redness, foreign body sensation	Re-surgery- stem cell grafting immediately at presentation on PoD 7	07 days
Recurrence	01	Regrowth of pterygium	Re-surgery at presentation on PoD 45	14 days

*PoD: Post-operative day.

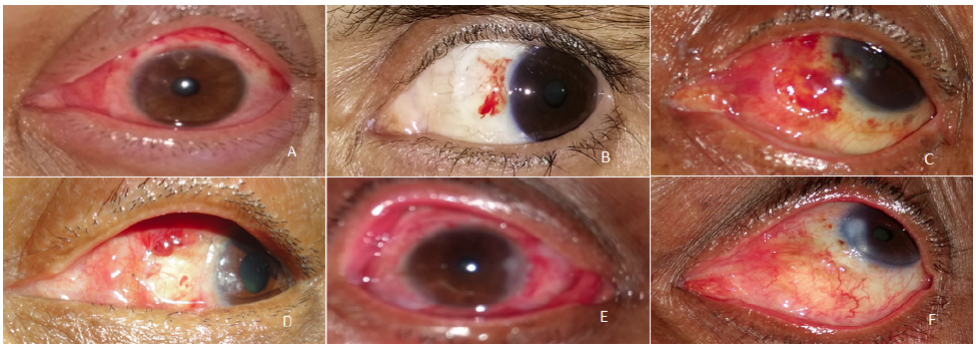

Figure 12: Post-operative complications in different patients: A- Sub-amniotic membrane edema on day 1; B- Small sub-amniotic membrane hemorrhage on day 1; C- Large sub-amniotic membrane hemorrhage on day 1; D- Granuloma formation on day 15; E- Loss of stem cell lenticules and BCL on day 7; F- Signs of early recurrence on day 21.

increasing the frequency of corticosteroid (Figure **12A**). The edema resolved in two weeks. In two patients, sub- amniotic membrane hemorrhage was seen (Figures **12B** and **C**). These patients were started on chewable tablet Vitamin C 500 milligrams thrice a day. By day 21 follow-up, the hemorrhage had resolved. In three patients, the BCL was found displaced on day 7 and immediate BCL replacement was done at the time of presentation. In 2 patients on day 7 follow-up, retraction of the amniotic membrane graft was seen. As the retraction was mild and without the exposure of bare sclera, so patients were managed conservatively by increasing the frequency of lubricant. Two patients showed signs of early recurrence and presented with formation of an inflammatory fibrovascular tissue at the graft site. The patients were managed by increasing the frequency of corticosteroid and were monitored for any increase in the size of inflammatory fibrovascular tissue. The inflammation resolved in both the patients in 2 months' time and none of the two patients progressed to recurrence in the follow-up period of 6 months. Granuloma formation at the graft site was seen in one patient on day 15 and was managed by increasing the frequency of corticosteroid (Figure **12D**). Re-surgery was planned in two patients. Loss of stem cells lenticules was observed on the graft site on day 7 in one patient and immediate stem cell re-grafting was done (Figure **12E** and **F**). The patient showed signs of good healing by day 14 (Figure **13**). One patient who had non-compliance with topical medications and had missed all follow-up consultations, presented on day 45 with actual recurrence of excised pterygium (Figure **14A**). The patient was immediately planned for surgery and a revision of the focal-SLET procedure was done. On subsequent follow-up, the patient did not show any signs of recurrence again (Figure **14B**).

Upon determination of outcome at the end of our follow-up period, 22 (57.89%) patients did not require

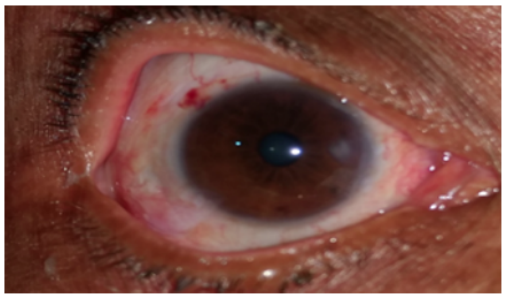

Figure 13: Patient in figure 12E after re-grafting of amniotic membrane with replacement of stem cell lenticules on post-op day 7 after re-surgery.

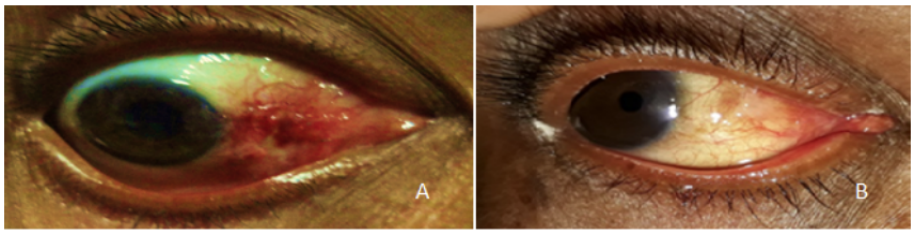

Figure 14: A- Complete recurrence of pterygium in one patient on day 45. B- The same patient after re-surgery.

any form of intervention other than the prescribed post-operative medications. 14 (36.84%) patients required medical intervention either in the form of increase in frequency of the topical drug or replacement of BCL. One (02.63%) patient required re-surgery for replacement of stem cell lenticules. An unsatisfactory outcome was observed in only one patient who required total revision of the procedure (Figure **15**).

DISCUSSION

The current gold standard in pterygium treatment is CLAu as first described by Kenyon and Tseng, in which virgin conjunctiva and adjacent limbus are taken from the same eye and transplanted onto the bare sclera [9]. However, the procedure becomes challenging when the size of pterygium is large and a sufficient donor graft cannot be obtained without disturbing the ocular surface morphology [15]. Preservation of virgin conjunctiva is also prudent for success of glaucoma surgery if required in future. An alternative technique of cultivated limbal epithelial transplantation was described by Pelligrini *et al.* to treat LSCD, where *in vivo* cultivation of limbal stem cells, preparation of grafts and their subsequent transplantation was done [16]. The procedure has the advantage of preserving virgin conjunctiva but it is expensive and requires considerable expertise with an elaborate laboratory setup for cultivation of stem cell graft. The high procedural costs also render it difficult to be made accessible in small hospitals and remote areas. A modification of this procedure using amniotic membrane as bed for cultivation of grafts has also been successfully used in patients [17, 18]. But this procedure also has the same associated difficulties as that described by Pelligrini. Since Sangwan *et al*, in 2012, successfully showed promising results with autologous SLET in ocular surfaces damaged due to chemical burns, the procedure has become a benchmark for treating LSCD. As pterygium too is a disorder of LSCD, a modification of the technique described by Sangwan *et al.* has been reported in 10 patients with considerable success in pterygium excision surgery by Hernández-Bogantes *et al.* [12]. Sati *et al* in 2019 presented a study comparing the efficacy of mini-SLET vs CLAu in primary pterygium

Figure 15: Outcome.

Grading	Definition	Intervention	Number of patients
Very Satisfactory	No secondary intervention required	None	22 (57.89%)
Satisfactory	Some form of intervention required	Medical intervention	14 (36.84%)
		Surgical intervention	01 (02.63%)
Unsatisfactory	Graft failure	Re-surgery	01 (02.63%)

treatment wherein 40 participants with grade 2 nasal pterygium (as per Tan *et al.*) underwent the mini-SLET procedure [19]. In our study, a minimum limbal involvement of 5 mm in primary nasal pterygia of grade 2 or more was kept as a standard criterion for participant selection to provide uniformity.

The most common presenting age group in both the studies, similar to our study, was the fifth decade of life [12, 19]. A majority 86.83% of patients in our study presented before the end of sixth decade of life.

The study groups in the analyses by both Hernández-Bogantes *et al* and Sati *et al.* had male preponderance in comparison to our study, which had female preponderance [12, 19]. This could be attributed to the local economic and cultural practices of the Central Indian region wherein the females of the family also contribute to the total income of the household.

All the participants in our study belonged to rural background and were either farmers or laborers. A preponderance in outdoor activities too was seen in 70% of patients in the study by Sati *et al*. [19]. This was consistent with a prolonged exposure to sunlight which ultimately causes increased exposure to ultraviolet radiation.

The most common reason for surgery in our study was cosmetic in 55.26% of patients as was in the study by Sati *et al* where 37.5% patients opted for surgery due to cosmetic concerns [19].

The study by Hernández-Bogantes *et al.* did not provide any reference as to the size of the pterygium tissue [12]. In the study by Sati *et al.*, the uniform criterion for surgery was 2 mm extension of the pterygium onto the cornea. But even in this study the extent of vertical limbal involvement was not considered [19]. This is of significance as the size of graft to be transplanted correlates directly with the height of limbal involvement by pterygium tissue. Our study is unique in this respect because we have observed that size of primary pterygium is the most important determinant when considering between CLAu and focal-SLET. As large size pterygium excision demands a larger graft, human amniotic membrane grafting with focal limbal epithelial transplantation has been used as an alternative to CLAu. The human amniotic membrane has stem cell characteristics and anti-inflammatory, anti-fibrotic, and immunomodulatory properties [20]. These properties make hAM an ideal substitute in pterygium over conjunctival autografting. The patients experience less discomfort after hAM transplantation due to its anti-inflammatory action. The patients' recovery time is reduced as no bare areas are left as with conjunctival autografting [21]. It has been observed in multiple research studies that grafting with hAM alone leads to a higher rate of recurrence than CLAu, so, focal limbal stem cells transplantation is done over the hAM graft to treat the limbal stem cell deficiency [22].

Preservation of virgin conjunctiva is justified for patients with limited conjunctiva as those with large pterygium, history of multiple surgeries, and in glaucoma suspects. An important advantage of the procedure is also its repeatability. As human amniotic membrane is used rather than nascent conjunctiva and only a thin strip of ipsilateral healthy limbal tissue is used in the procedure, focal-SLET is an excellent candidate for revision surgery in patients with recurrence.

36.84% of participants in our study presented with pterygium where limbal width was >8.0 mm and of these 85.71% were Grade 2 pterygium. From this we can conclude that higher grading of pterygium does not correlate with more width at limbus. None of the grade 4 patients showed more than 7.0 mm of limbal involvement supporting that progressive, rapidly growing pterygia have more linear than angular growth.

The surgical technique employed in the studies by Hernández-Bogantes *et al.* and Sati *et al.* is pterygium excision with subsequent placement of hAM graft over bare sclera, tucking of graft under the nascent conjunctival margins and ipsilateral limbal epithelial transplantation [12, 19]. We employed a technique of reverse peeling of pterygium with the rest of the steps being the same as employed in other studies.

Patients were evaluated for any post-operative complaints only in the study by Sati *et al*. [19] The frequency and duration of post-operative complaints of pain, lacrimation and foreign body sensation, observed in their study group were similar to those that were observed in our study group. The complaints persisted for a period of 7- 14 days post-operatively, similar to our study.

On follow-up, out of the 16 participants that presented with post-operative complications, 6 (37.50%) presented with complications like sub-amniotic membrane edema and sub-amniotic membrane hemorrhage. These are expected post-operative complications and could be a result of localized inflammatory reaction to the fibrin glue

leading to edema, or improper cauterization of episcleral vessels leading to hemorrhage. The post-operative complications observed in the other 10 (62.50%) participants were a result of poor-compliance, either with topical medications or proper ocular care. Displacement of the soft BCL in three, displacement of the hAM graft in two, and loss of stem cell lenticules in one of these participants were a result of frequent rubbing of eyeball. Early signs of recurrence in two, and granuloma formation were observed in one of these 10 participants who gave a history of non-compliance with their topical medications. Total recurrence was observed in only one out of these 10 patients which was a result of complete discontinuation of topical medications.

Recurrence in one patient was also observed in the study by Sati *et al.* upon follow-up at 6 months while none of the 10 patients in the study by Hernández-Bogantes *et al* showed signs of recurrence till 8 months of follow-up [12, 19]. The revision surgery done after recurrence was CLAu in the study by Sati *et al*, while we performed a revision surgery of focal-SLET in the only patient who developed recurrence [19]. On subsequent follow-up, the patient did not develop any signs of recurrence and this is a testament to the efficacy and reproducibility of this procedure.

CONCLUSION

Surgical excision of large nasal pterygia requires replacement with a large graft that has the same physiological properties as that of the conjunctiva. Conventionally, a conjunctival autograft from the same eye would be transplanted over the excised pterygium site. The technique of focal-SLET can be considered as the alternative procedure of choice for patients with large pterygia. This procedure preserves the virgin conjunctiva of the patient, cures the limbal stem cell deficiency which was responsible for the pterygium in the first place, causes less discomfort after surgery due to the inherent properties of amniotic membrane, and can be done again as revision surgery in patients presenting with complications. Further randomized controlled trials in multiple centers with longer follow-up periods could validate the results of our study.

ABBREVIATIONS

CLAu: Conjunctival Limbal Autograft

CS: Corticosteroid

hAM: Human amniotic membrane

LSCD: Limbal stem cell defect

PoD: Post-operative day

SLET: Simple limbal epithelial transplantation

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