Original Article

A comparative study of tarsorrhaphy and amniotic membrane transplantation in the healing of persistent corneal epithelial defects

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Purpose: To compare and study the clinical outcome of tarsorrhaphy and amniotic membrane transplant in the healing of persistent corneal epithelial defects in terms of clinical improvement and symptomatic relief. **Methods:** This was an interventional, prospective study in which a total of 60 patients with persistent epithelial defects (PED's), randomly divided into two groups of 30 patients each who underwent tarsorrhaphy (Group A) or amniotic membrane transplantation (Group B) with a 4-week-follow-up period, were included. The main parameters studied were the size of an epithelial defect, total healing time, pain score, and complications. **Results:** The study included 60 eyes of 60 patients with PED. The healing time was 9.83 ± 6.51 days in Group A (median = 9.50 days, IQR = 1–7 days) vs. 18.33 ± 13.46 days (median = 19.50 days, IQR = 1–21 days) in Group B. A total of ten eyes (16.7%) did not heal at the end of 4 weeks. **Conclusion:** There was a significant reduction in the area of epithelial defect at the end of the 1 week and 2 week follow up postoperatively, in both the treatment forms. The mean healing time in patients of Group A was less as compared to that of the patients in Group B.

Key words: Amniotic membrane transplantation, human amniotic membrane, persistent epithelial defects, tarsorrhaphy

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The human cornea accounts for roughly two-third of the total refractive power of the eye. An injury to the corneal epithelial surface results in an epithelial defect which usually heals quickly but when they cease to heal within 2 weeks, they are termed as persistent epithelial defects (PED's).[1] The standard therapies in the treatment of PEDs include artificial lubrication, discontinuation of toxic medications, punctal closure, bandage soft contact lens (BCL), debridement, and tarsorrhaphy. The newer therapies consist of amniotic membrane grafting, autologous serum, whole blood-derived products, limbal stem cell transplantation, thymosine beta 4, nexagon, and scleral contact lenses.[2] The present study aims to compare and evaluate the clinical outcomes of tarsorrhaphy and amniotic membrane transplant in the healing of persistent corneal epithelial defects and subsequent corneal vascularization if any thereby providing symptomatic relief.

Methods

This was an experimental study conducted over a period of 12 months which included 60 eyes of 60 patients by convenient sampling method. The subjects for the study were taken from the out-patient and in-patient departments.

Inclusion criteria

All patients with PEDs were included in the study. The various etiologies responsible for the PEDs included exposure keratopathy, post penetrating keratoplasty (PK), and trauma. All these patients were taken up for the respective procedures after instituting a maximum medical therapy and patching or BCL application for at least 2 weeks. The epithelial defects which did not heal on the above-mentioned therapy were labeled as PEDs and were included in the study.

Exclusion criteria

All patients with duration of epithelial defects less than 2 weeks, patients who were healed through medical therapy, severe LSCD, acute anterior segment infection or associated lid pathology, ocular surface disorders, painful bullous keratopathy, cases where intraocular pressure (IOP) was >21 mmHg, patients on long-term immunosuppressant drugs and repeated PK surgeries were excluded from the study.

Written informed consent was taken from the patient (or the patient's parents in case patient was less than 18 years) before including them in the study. Permission from the ethical committee was also obtained. These patients were randomly divided into two groups using envelope technique (Group A and Group B) of 30 eyes each. Patients in group A underwent tarsorrhaphy and the patients in group B underwent AMT. Demographic indices were included in the case recording form. Clinical assessment of the patients

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were done against predecided parameters. A detailed history of present illness and past history was recorded. The ocular examination included best-corrected visual acuity (BCVA) done on Snellen's visual acuity chart and later converted to logarithm of minimum angle of resolution (logMAR), IOP readings with a noncontact tonometer or tonopen were taken wherever possible. Anterior segment evaluation was done using a Carl Zeiss Meditec AG slit lamp and the central fundus was seen with the help of a Heine beta 200 direct ophthalmoscope or an indirect ophthalmoscope. In cases where fundus was not visible due to poor media clarity, B-Scan ultrasonography was performed using Nidek Echoscan US-4000.

The size of the epithelial defect, pain score, and the extent of vascularization of cornea was assessed preoperatively and postoperative follow-up assessment was carried out on the postoperative day 1, week 1, week 2, and week 4. The size of epithelial defect was recorded as the area of the cornea affected by the epithelial defect. It was calculated by measuring the length and the breadth of the PED (in mm) using the slit beam lamp bio-microscope and later multiplying the two entities. The area of PED was calculated in mm^2. The extent of vascularization was recorded in the number of quadrants and type as superficial or deep. The symptoms of photophobia, lacrimation, and foreign body sensation were recorded.

The type of surgical modality performed was recorded (tarsorrhaphy/AMT). Further, the type of tarsorrhaphy (permanent/temporary) and site of tarsorrhaphy (central/para-median) was noted.

Procedure Tarsorrhaphy was performed by first injecting local anesthesia (2% xylocaine) in the upper and lower lids. A raw area was created on the inter-marginal strip using number 11 blade. The raw area measured 2mm × 5mm both on the lower and upper lids. The location of the same (para-median, median or lateral) was decided as per case and was sutured using 5-0 non-absorbable suture along with bolsters.

In cases where AMT was performed, the type of amniotic membrane used (fresh, cryopreserved, and commercially available) was recorded. The technique used was mentioned as either inlay, graft/overlay, patch/filling, or layered technique. The AMT stay was recorded in number of days.

Procedure

The stromal surface of the amniotic membrane was identified by the presence of vitreous such as strands using a cotton bud. All the debris over the corneal surface were removed prior to the graft placement with the help of the cotton bud. Loose epithelium over a PED was also removed using small fine forceps. The graft was placed over the defect and spread out with the help of an iris repositor or a rod. The size of the defect was measured with calipers and graft of appropriate size was cut in accordance. The size of the graft was kept at least 1 mm larger than the defect and 10-0 nonabsorbable nylon sutures were placed circumferentially or parallel to the cut edge in an interrupted or continuous purse-string manner. A bandage contact lens was applied over the amniotic membrane. The total healing time taken was recorded along with relief in the prerecorded symptoms. Preoperative and postoperative pictures were taken. Any complications related to tarsorrhaphy or AMT were recorded. Pain score index: pain perceived was recorded on a scale from grade 0–4 as described by the patient. Grade 0 - No pain, Grade 1- Mild pain, Grade 2- Moderate pain, Grade 3- Severe pain, Grade 4- Unimaginable pain.

Statistical analysis

All continuous variables were described as mean ± standard deviation or median with interquartile range (IQR) and categorical variables were expressed as proportions. Group differences in continuous variables were analyzed using the Student *t*-test for normally distributed variables and the Mann-Whitney U test for nonparametric variables. The normality of distribution was tested using the Konglomerat Smirnov test. Group differences in categorical variables were analyzed using the Chi-square or Fischer's exact test. The vision was measured in Snellens equivalent and was converted to logarithm of minimum angle of resolution (logMAR) for statistical analysis.

Results

The present study included 60 eyes of 60 patients during the study period, with 30 eyes receiving tarsorrhaphy (Group A) and the remaining 30 receiving AMT (Group B). The demographic indices and the preoperative parameters are described in Table 1 along with the comparison between the two groups in Table 2.

In the present study, 15 (25%) eyes had PED due to exposure keratopathy, 32 (54%) secondary to PK, 5 (8%) due to trauma, and 5 (8%) were idiopathic.

Out of 30 eyes that underwent tarsorrhaphy, 27 (90%) had a permanent tarsorrhaphy and 3 (10%) had a temporary tarsorrhaphy. The tarsorrhaphy was removed after a mean ± SD of 52.1 ± 47 days (median = 26 days, IQR- 18–78 days, range = 6–171 days).

Out of the 30 eyes that had AMT, 20 (71%) had fresh AMT, 5 had cryopreserved AMT, and 5 had commercial available AMT

Table 1: Demographic indices and preoperative parameters

Variables	Group A (N%)	Group B (N%)	*P*
Age (Years) (mean±SD)	48.3±18.6	48.1±18.4	0.95
Gender			
Males	25 (83.3%)	27 (90%)	
Females	5 (16.7%)	3 (10%)	0.58
Residence			
Rural	18 (60%)	22 (78%)	0.09
Urban	12 (40%)	8 (26.7%)	
Habituations			
Smokers	14 (46.7%)	13 (43.3%)	0.79
Variables	**Group A (Mean±SD)**	**Group B (Mean±SD)**	***P***
BCVA (logMAR)	1.16±0.73	1.30±0.51	0.38
RBS (mg/dl)	102±22	115±27	0.06
Size of PED (mm^2)	26.57±24.55	34.90±30.136	0.245
Duration of PED (days)	20.6±4.9	19.4±4.1	0.44

transplantation. The sutures securing the AMT were removed after a mean ± SD of 15.7 ± 5 days (median = 15.5 days, IQR = 12–20 days) and the AMT lasted for a mean duration ± SD of 22.6 ± 7 days (median = 23.5 days, IQR = 17.5– 27.5 days).

The healing time was 9.83 ± 6.51 days in Group A (median = 9.50 days, IQR = 1–7 days) vs. 18.33 ± 13.46 days (median = 19.50 days, IQR = 1–21 days) in Group B.

The comparison of healing characteristics in the form of size of the epithelial defect and the corneal vascularization between the two groups at various follow-up periods have been described in Tables 3 and 4, respectively. A total of ten eyes (16.7%) did not heal at the end of 4 weeks, out of which seven eyes (23.3%) were from Group B and three eyes (10%) were from Group A. Moreover, smokers showed a trend of delayed healing. It was also observed that patients with associated systemic comorbidities such as diabetes (although controlled on medications) also showed delayed healing. Furthermore, the eyes that did not heal showed a positive association with smoking (*P*-value = 0.04). All the patients who did not heal were smokers and four of them were diabetic patients.

Table 2: Comparison of preoperative symptomatology and signs between the two groups

Variables	Group A (N%)	Group B (N%)	*P*
Symptoms			
% Photophobia	30 (100%)	30 (100%)	0.99
% Lacrimation	29 (97%)	30 (100%)	0.53
% Foreign body sensation	30 (100%)	30 (100%)	0.99
Pain Score			
No Pain	2 (6.7%)	0 (0%)	0.59
Mild pain	11 (36.7%)	9 (30%)	
Moderate pain	15 (50%)	16 (53%)	
Severe pain	1 (3.3%)	3 (10%)	
Unimaginable pain	1 (3.3%)	2 (6.7%)	
Corneal vascularization			
0 Quadrant	28 (93.3%)	22 (73.3%)	0.53
1 Quadrant (Superficial)	2 (6.7%)	6 (20%)	
2 Quadrant (Superficial)	0 (0%)	2 (6.7%)	

Table 3: Comparison of area of epithelial defect at various follow up time points between Group A and Group B

Time point	Group A (mm²)	Group B (mm²)	*P*
Preoperative	26.57±24.55	34.90±30.16	0.24
1 day	25.33±25.03	31.37±30.22	0.40
1 week	11.67±18.21	21.97±25.51	0.04
2 weeks	1.3±2.54	9.63±15.78	0.00
4 weeks	1.43±4.67	3.97±7.38	0.12

Discussion

In the present study the (mean ± SD) duration of the epithelial defect was for 20.1 ± 4.5 days (median = 19 days, IQR = 16–22 days). The mean duration of an epithelial defect in a study conducted by Blanco *et al*. was 8.1 weeks[3] and by Prabhasawat *et al*. was also longer about 5.45 weeks.[4] Since they had to manage other complications such as raised IOP, scarred ocular surface, integrity of the ocular surface and so on both medically and surgically, the mean duration of an epithelial defect was longer. This was not the case in the present study as all these confounding factors were excluded that may interfere with the healing of the PED.

In the present study, 15 (25%) eyes had PED due to exposure keratopathy, 32 (54%) secondary to PK, 5 (8%) due to trauma, and 5 (8%) were idiopathic. Overall, the predominant etiology of PED in a study conducted by Prabhasawat *et al*. was neurotrophic ulcer 75% followed by LSCD at 15% and lastly exposure keratitis at 10%.[4] Whereas higher incidence of ocular surface disorders (26.7%) and other as miscellaneous causes were studied by Hamza *et al*.[5] The major etiology in a study conducted by Blanco *et al*. was PED associated with stromal thinning or corneal ulcers.[3] Seitz *et al*. on the other hand conducted a study purely on PED post PK.[6] Rahman *et al*. included all cases of nonhealing corneal ulcers.[7] The predominant etiology in a study conducted by Moin *et al*. was infectious keratitis (50%) followed by PED due to exposure of keratitis and neurotrophic ulcers.[8]

In the current study, the mean area (± SD) of the epithelial defect preoperatively was 30.74 ± 27.34 mm². This varied from 26.57 ± 24.55 mm² for patients in Group A. This was to 34.90 ± 30.14 mm² for patients in Group B. The difference between the preoperative sizes of the epithelial defect was statistically nonsignificant between the two groups hence making them comparable with no bias. This preoperative size

Table 4: Comparison of vascularization between Group A and Group B

	No vascularization		1 Quadrant		2 Quadrants		3 Quadrants		4 Quadrants	
	Sup	Deep	Sup	Deep	Sup	Deep	Sup	Deep	Sup	Deep
2 weeks										
A	9 (30%)	29 (96.7%)	19 (63.3%)	1 (3.3%)	2 (6.7%)	0	0	0	0	0
B	0	7 (23.3%)	9 (30%)	22 (73.3%)	19 (63.3%)	1 (3.3%)	2 (6.7%)	0	0	0
4 weeks										
A	0	29 (96.7%)	23 (76.7%)	0	7 (23.3%)	1 (3.3%)	0	0	0	0
B	0	3 (10%)	4 (13.3%)	21 (70%)	13 (43.3%)	6 (20%)	11 (36.7%)	0	2 (6.7%)	0
P	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

of the PED in the present study was larger than the average size of PED included by Seitz *et al*. in their study. The mean dimensions of the defects due to erosions in the above study was 4.2 ± 1.9 mm × 3.3 ± 2.3 mm (13.86 ± 4.37 mm^2) and due to ulcers was 3.5 ± 2.2 mm × 3.0 ± 1.7 mm (10.5 ± 3.74 mm^2).[6] Prabhasawat *et al*. also included cases with smaller preoperative epithelial defect sizes in their study with the average size being 3.8 mm in the largest meridian. They did not evaluate the complete area of the epithelial defect.[4]

There was a significant reduction in the total area of epithelial defect at all postoperative follow-up periods when compared with the preoperative size as well as when compared with the previous postoperative follow-up on day 1, 1 week, 2 week, and 4 week (*P*-value = 0.00). There was a statistically significant difference in the reduction in the size of epithelial defect at postoperative follow up of 1 week (*P*-value = 0.04) and 2 weeks (*P*-value = 0.00) between the patients of the two groups. It was observed that though the size of PED reduced significantly in both the groups it reduced at a statistically faster rate among the patients of Group A than Group B.

It was observed that among the patients in Group B, the ones treated with fresh and cryopreserved amniotic membrane appeared to heal faster as compared to the cases which were treated with a commercially available membrane. However, the difference was not statistically significant. This can be explained by the fact that the commercially available amniotic membrane acts only as a scaffold while the freshly prepared and the cryopreserved probably contribute in the form of various growth factors in addition to acting as a scaffold. However, the review of literature provides no conclusive study to support the above observation.

The patients in Group A healed at 9.83 ± 6.51 days in Group A (median =9.50 days, IQR = 1-7 days) vs. 18.33 ± 13.46 days (median = 19.50 days, IQR = 1–21 days) in Group B. Even though the suture removal in Group B patients was performed at 15.7 ± 5 days the residual amniotic membrane was still secure in place with the BCL. Moreover, it is clearly evident that the patients in Group A healed before the suture removal was in the patients in Group B. The defects in Group B also healed but later as in comparison with group A at 18.33 ± 13.46 days (median = 19.50 days, IQR = 1–21 days). There were no cases in which the PED recurred after removal or spontaneous dissolution of the amniotic membrane or removal of tarsorrhaphy.

The patients in Group A probably healed faster as the eyelids remain closed and the cornea is least exposed to the outer environment and remains in contact with the eye's own tissues such as the conjunctiva. Since the palpebral aperture is nearly closed, instillation of topical medications also remains *in-situ* for a longer period of time and aid in healing faster. The deleterious effects of the constant blinking mechanism that may erode the newly formed corneal epithelium are also surpassed.

Among all the 60 patients included in the present study, 2 (3.3%) patients did not have any complaint of pain at presentation, 20 (33.3%) had mild pain, the majority of 31 (51.7%) had moderate pain, 4 (6.7%) patients presented with severe pain, and only 3 (5%) patients presented with unimaginable pain. A significant reduction in the pain score was observed at the follow-up day 1 and week 1 (*P*-value = 0.02, 0.00 respectively) in both the groups. At the end of 4 weeks follow-up a total of 48 (80%) had no pain, 10 (16.3%) complained of mild pain, and 1 (1.7%) each complained of moderate and severe pain. There was no patient still complaining of unimaginable pain at the end of the 4 weeks follow-up, even if the defect did not heal.

In the study conducted by Hamza *et al*., 3 (10%) patients did not complain of any pain, 6 (20%), 7 (23%), 13 (43.3%), and only 1 (3.3%) case had mild, moderate, severe and unimaginable pain, respectively. After 1 month of follow up after AMT most of the patients, 25 (83.3%) had no pain, only 2 (6.7%) and 3 (10%) described mild and moderate pain, respectively. These results were comparable to our study suggesting that AMT was a good technique to target the symptomatology and to alleviate the pain caused by PED.[5]

In the present study, however, we observed alleviation of pain was seen to be statistically significantly faster in patients from Group A than Group B. On analyzing, it may be due to the persistent foreign body sensation and mild discomfort as a result of application of sutures and application of bandage contact in the patients in Group B.

The majority of the patients 50 (83.3%) had no pre-existing corneal vascularization when examined preoperatively, remaining ten patients had superficial vascularization of which eight (13.3%) were presented in first quadrant and 2 (3.3%) in second quadrants. There was progressively increasing vascularization both superficially and deep along with the healing response as seen at various follow-up time points. There was significant vascularization (*P*-value = 0.00) along the entire postoperative follow-up course depicting a positive healing response among patients in both the groups. It was also observed that there was predominant superficial vascularization among patients of Group A and both superficial as well as deep vascularization among the patients in Group B.

It has been shown that amniotic membrane contains higher levels of growth factors such as hepatocyte and transforming growth factors which modulate proliferation and differentiation of stromal fibroblast and promotes deep vascularization.[9]

In the current study, symptoms of photophobia, lacrimation, and foreign body sensation were present in 60 (100%), 59 (98.3%), and 60 (100%) cases, respectively when examined preoperatively. Only 9 (15%), 13 (20%), and 12 (15%) patients complained of photophobia, lacrimation, and foreign body sensation, respectively concluding significant reduction of symptoms by employing both treatment modalities. In a study conducted by Hamza *et al*. in 2011, 27 (90%) of the patients were photophobic preoperatively. At the end of the study only 4 (13.3%) patients still complained of photophobia.[5]

Conclusion

There was a statistically significant reduction in the area of epithelial defect at the end of week 1 and week 2 follow-up

postoperatively in both the treatment forms. The mean healing time in patients of Group A was less compared to that of patients in Group B and was statistically significant. Habituations such as smoking delayed the healing of the PED. It was also noted the patients with comorbidities such as uncontrolled diabetes mellitus also retarded the healing process. Corneal vascularization, as an indicator of healing, progressively increased along the entire course of postoperative follow up. Patients in Group A ended up developing only superficial vascularization whereas the patients in Group B had both deep as well as superficial entities. Pain score also reduced subsequently along the follow-up period with drastic reduction at first follow-up day and at the end of week 1 with both the treatment forms. Both the treatment modalities significantly reduced the symptomatology associated with the PED by the end of the study. Only 10 out of 60 patients did not heal at the end of the study. Three patients were from Group A and seven were from Group B.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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