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BOWMAN'S MEMBRANE LENTICULE TUCK-IN: A NOVEL CONCEPTUALIZATION FOR THE MANAGEMENT OF POST INFECTIOUS CORNEAL ULCERS AND PERFORATIONS

Dr Dharamveer Singh Choudhary	MBBS, MS Associate Professor, Ophthalmology,S.M.S. Medical College, Jaipur
Dr Pratibha Choudhary	Dept. Of Ophthalmology, SMS Medical Colledge Jaipur
Dr. Siddharth Maanju	Dept. Of Ophthalmology, SMS Medical College, Jaipur
Dr Gargi Verma	Counsaltant Dept. Of Ophthalmology, SMS Medical College, Jaipur
Professor Kishor Kumar	Professor Ophthalmology, SMS Medical College, Jaipur
Dr Anamika Chaudhary*	*Corresponding Author

ABSTRACT **PURPOSE:** To evaluate a new surgical modality of using bowman's membrane for the management of non-healing post-infection (after infection is resolved) ulcers including perforations.**METHODOLOGY:** A total of 17 eyes of 17 patients who suffered corneal infection and the resultant ulcer did not heal after infection was over, were included and underwent surgical process where a donor bowman's membrane was harvested and fashioned according to the lesion and tucked inside the ulcer after making a recess in anterior one third of stroma all around 360 degrees. The surface was also supplied with limbal stem cells taken from same eye from different location to quicken the epithelization process. Primary outcome measured were healing (stable epithelization at 6 months) and improvement in best corrected visual acuity (BCVA).**RESULTS:** A total of seventeen patients, with ten females and seven males were recruited. The mean age with standard deviation was 52.705 ± 16.513 years. Mean epithelization time in weeks with standard deviation was 3.470 ± 0.977. The mean Ulcer size along their longest axis and the axis perpendicular to it in mm was 3.4× 3.3 ± 0.59. The pre-operative mean BCVA was 0.0376 ± 0.051 Decimal units and the post- operative improved BCVA was 0.219 ± 0.16 Decimal units suggesting a significant improvement (P value <0.0001). Mean preoperative Corneal thickness value was 148.82 ± 110.127 microns and the postoperative value was 402.94 ± 46.59 microns which was significantly better (P < 0.0001)**CONCLUSION:** Donor bowman's membrane lenticule tuck-in for neurotrophic ulcers is a safe and highly effective treatment and requires minimal instruments and expertise

KEYWORDS : Bowman's membrane lenticule, Corneal transplantation, Graft tuck-in, Ulcer recess

INTRODUCTION

Corneal ulceration is defined as a corneal infiltrate associated with an overlying epithelial defect and it's a vision threatening medical condition presenting in all age groups and either sex that varies in morbidity worldwide[1]. A nonhealing corneal ulcer is defined as an ulcer which does not show any indication of healing within two weeks, despite the administration of proper medical treatment[2]. It is one of the major ocular emergencies causing ocular morbidity. It is considered a leading cause of corneal blindness especially in the developing countries. It has been estimated that globally, corneal ulceration with ocular trauma are resulting in 1.5 -2 million cases of corneal blindness annually[3]. Suspicious causes of a nonhealing corneal ulcer include persistent infection, neurotrophic keratopathy, exposure keratopathy, dry eye, treatment toxicity, steroid use, and chronic conjunctival inflammation, such as ocular cicatricial pemphigoid[4].

In this study we take into consideration cases of post infectious non healing ulcers and small perforations. The problem being that once a corneal ulcer occurs and is left unattended, corneal melting, descemetocele, and corneal perforation can subsequently develop, leading to site threatening consequences[5]. Also, a resistant corneal ulcer progressively develops in which case lamellar keratoplasty or penetrating keratoplasty is usually needed [6][7]. Therefore, curing a resistant ulcer in its early stages is highly recommended.

Anatomically, the cornea is innervated by the branches of the trigeminal nerve which plays paramount role is maintaining ocular surface of the eye. Ulcers cause corneal denervation which detrimentally affect vitality, metabolism, ocular surface health. All this leading to the disruption of the microstructure of the eye causing loss of microvilli intracellular edema abnormal basal lamina and finally inability of the ulcer to heal. These kinds of ulcers have a very peculiar picture, the ulcer has recurrent epithelial breakdown and poor wound healing in spite of treatment leading to the formation of a neurotrophic ulcer. Gradually the situation takes a turn for a worse which leads to vision loss, constant watering, recurrence of infection, recurrent glaucoma, endophthalmitis, panophthalmitis, autoevisceration, etc.

The disease has a multifactorial nature for which various treatments have been devised and improvised but none so efficacious enough thus leaving us with limited success with the treatment of the disease and causing recurrence or worsening of the disease. Medical therapy remains the cornerstone of treatment followed by surgical modalities if there occurs no improvement or worsening of the disease. Surgical procedures like corneal gluing, bandage contact lens, conjunctival flap, tarsorrhaphy, amniotic membrane and corneal transplantation can be opted for[8-12]. There are problems akin to all of the prevalent treatments, Gluing is done only after perforation and is very irritating, BCL carries the risk of flare up of infection, conjunctival flaps and amniotic membrane transplantations are stop-gap managements and tarsorrhaphy is generally done in neurotropic ulcers. Furthermore, even after all these efforts there may be recurrences and treatment failure, thus, newer modalities need to be researched for.

SMILE has been used to obtain a thin stromal lenticule which can be overlayed on the ulcer and has shown documented success [16] but needs larger studies and is neither strong not thick and so suitable for only superficial ulcers.

Observing the above modalities and increased frequency of resolved ulcers converting into non-healing ulcers attended with further risks, we have devised and developed a new surgical technique to heal these ulcers by tucking bowman's membrane lenticule in the recess covering corneal ulcer and have assessed its efficacy in non-healing neurotrophic ulcers. This lenticule being very strong, transparent and innate structure will provide strength to cornea, help granulation tissue

formation beneath and rapid epithelisation over it. The epithelisation will also be upscaled by the limbal biopsy cells pasted over the membrane. The use of such lenticule has been seen with reasonable success for the stabilization of advanced keratoconus cases[17,18] and in perforated corneal ulcers[19].

METHODOLOGY

The study was a hospital based prospective, non-comparative type of interventional study was conducted between April 2018 to December 2020 on the patients admitted in tertiary care medical college in Rajasthan, India. The study was started only after proper approval from ethical committee. The patients were then explained the study process, the follow up, the risk- benefits of the study, the investigative nature of the study and the surgical complications of the study and only after they approved a proper informed and written consent was taken and then were enrolled for the study. In the study 17 eyes of 17 patients of post infectious nonhealing patients not responding to medical therapy for at least two weeks and who were sterile for microbiological culture of the ulcer specimen were included in the study. Patients who had ulcer size of greater than 4.0 mm in any linear dimension, perforation more than 2.0 mm, active corneal infection, patients unwilling for surgery, or those unable to come for follow up were excluded from the study.

After enrolment ocular examination was done slit- lamp examination, best corrected visual acuity (BCVA), ulcer size noted along its greatest dimension and the axis perpendicular to it, ulcer thickness, corneal sensations with the help of a cotton fibre were done as a part of the initial examination. All the surgeries were done by a single surgeon and the corneal tissues (only therapeutic grade tissue) were procured from a certified eye bank from which the bowman's membrane was harvested.

Surgical technique (Figure 1 & 2)

The procedure was done under peribulbar anaesthesia in the operation theatre. Firstly, the ulcer bed was scrapped extremely with the help of a 15 number blade to remove any debris or loose and dead cells of the cornea which may prevent adherence of the graft. After that with the help of a crescent blade (Webel edge) a recess was made all around the ulcer edges. The depth of the recess was about anterior one thirds of the corneal thickness. The length of the recess depended upon the location of the ulcer, in centrally located ulcers a large recess of about 8-9 mm extending up to the periphery of the cornea was created while 2-3 mm for peripheral ulcers avoiding the pupillary area was made. The donor cornea (therapeutic grade cornea) was mounted on the disposable artificial chamber (Katana, USA) and the epithelium was scrapped of the donor cornea with the help of a 15 number blade and inject air between the layers of the cornea to separate the stroma form bowman's membrane. After this, the exposed bowman's membrane was stained with trypan blue dye (Sunways). Then a corneal trephine of suitable size was used to mark the bowman's membrane. After staining a nick was given at the bowman's membrane margin to lift up the edge of the membrane with the help of a crescent blade. Then the bowman's membrane is separated from the stroma with the help of a blunt instrument such as an iris repositor. Then with the help of a blunt forceps the membrane is held and stripped of the stroma. After harvesting, the edges of the membrane were trimmed a little larger than the dimensions of the ulcer and then placed the graft over the ulcer and tuck in the edges of the membrane in the recess that was created earlier after ensuring that the ulcer bed is debris free and dry and the wrinkles in the bowman's membrane are then smoothened out. A bandage contact lens was then placed over then eye and patched.

Postoperatively patients were started on eye drop moxifloxacin 0.5% QID dose, eye drop carboxymethylcellulose 1% QID, eye drop Atropine BID and a short course of oral prednisolone starting with 1mg/kg for one week and tapering it over 4 weeks. Topical steroids were started after epithelisation was complete and continued for 2 months.

Patient after the operation was followed up on day 1, week 2, week 4 and monthly till 6 months. On every visit epithelial healing was observed by staining with fluorescein, corneal thickness and any other complications were recorded. In the study, complete epithelization of the ulcer (i.e., negative fluorescein staining) with no recurrences up to 6 months was considered as success surgically.

STATISTICALANALYSIS

For the statistical analysis IBM SPSS software 22.0 version was used. Quantitative data were represented as mean standard deviation while qualitative data were expressed as percentage. Paired t test was used as a test of statistical significance for comparing preoperative and postoperative quantitative data. P value of <0.005 proved the significance of the results.

RESULTS (Table 1 & 2)

Seventeen eyes of 17 patients were enrolled (n=17), with females exceeding males. 07 were males (41%) and 10 were females (59%). The mean age of these patients with standard deviation was 52.705 ± 16.513. The mean age was suggestive of a relatively younger age group involvement. Mean epithelization time in weeks was 3.470 ± 0.977 which suggests a longer time taken probably because the ulcers were larger bowl shaped that took long time for granulation tissue to close the wound gap. The mean Ulcer size along their longest axis and the axis perpendicular to it in mm was 3.4× 3.3 ± 0.59. Five patients had small perforation plugged with iris tissue and psuedocornea or the granulation tissue. These were documented as comorbidity. Perforations were located in periphery in all but one case and therefore did not affect the eventual healing and visual outcomes. In one case, the perforation was near the visual axis and the visual outcome was poorer than others.

BCVA improved significantly in almost all cases. The pre-operative mean BCVA was 0.0376 ± 0.051 Decimal units and the post- operative improved BCVA was 0.219 ±0.16 Decimal units suggesting a significant improvement (P value <0.0001).

Corneal thickness was improved to almost near normal levels and contour. Mean preoperative value was 148.82±110.127 microns and the postoperative value was 402.94 ± 46.59 microns which was significantly better (P< 0.0001).

Table 1

Parameter	Mean ± SD	Percentage
Age	52.705 ± 16.513	
Sex	M- 7, F- 10	41.0 59.0
Epithelization time (weeks)	3.470 ± 0.977	
Ulcer size (mm)	3.4× 3.3 ± 0.59	
Comorbidity Perforation	05	

Table 2

Parameter	Pre-operative value (mean ± SD)	Post-operative value (mean ± SD)	P- value
BCVA	0.0376 ± 0.051	0.219 ± 0.16	<0.0001
Corneal thickness (microns)	148.82 ± 110.127	402.94 ± 46.59	< 0.0001
Corneal Ulcer size (mm)	3.4*3.3 ± 0.59		

DISCUSSION

Non healing ulcers have always been frustrating and tiring challenge for both patient and clinicians. So, it is important that the disease pathophysiology be understood thoroughly for proper and timely treatment. The cornea undergoes lots of trauma while combating an infectious pathology, specially fungal which although are slow growing but tends to stay for a long time (4 to 8 weeks generally) causing melting of cornea which further invite various cellular and immunological responses causing self-damage. This also damages other systems like tear functions, innervation etc which further jeopardises the healing systems[20,21,23]. Besides these factors, it has also been seen in some studies that an abnormal or deficient basal membrane caused by corneal melting due to local inflammation hindered epithelial healing, resulting in defective cellular adhesion and recurrent breakdown of the epithelium[23]. Also a cornea with an epithelial or basal lamina defect causes stromal deposition of the drug crystals used for the treatment of the disease which themselves cause a non healing ulcer[24]. So the essence of the problem in non-healing ulcers is epithelial defect and that active epithelial cells can markedly reduce ocular surface inflammation and relieve neurotrophic keratopathy[25,26] and perhaps other ulcers too. This is one of the reasons that even after intensive treatment modalities such as patching, scleral contact lens, cyanoacrylate glue, conjunctival flap, amniotic membrane transplantation and tarsorrhaphy the ulcers are relatively resistant to treat. As of now, amniotic membrane transplantation is a very successful method and has shown promise but due to low tensile strength, non-permanent, thin and non-transparent characters puts it in a temporary treatment only.

keeping all this in mind we have come up with an alternative that tries to encompass all the problems discussed above and which in our study

has given us concrete results. That being said bowman's membrane is a strong natural layer of the cornea about 10 to 20 microns in thickness (and increases and strengthens with age) that provides the much-needed reinforcement to the already thinned out cornea due to the disease unlike the amniotic membrane. Also, it provides a scaffold for nerve regeneration that helps in epithelial regrowth.

This capability of the bowman's membrane to restore the strength of the cornea has been demonstrated by Van Dijk et. al[17,18] who described the role of mid stromal Bowman layer transplantation in management of advanced keratoconus which delays progression of keratoconus and keratoplasty. Choudhary et. al[16] used bowman's membrane in cases of small perforation and the epithelialization of the wound was completed over a period of 2 weeks suggesting the role of the bowman membrane in epithelial healing. These results show similarity with our study where 17 eyes of 17 patients of non-healing postinfectious ulcer who underwent bowman's lenticule grafting and procedure was successful in all cases who remained healed up till the last follow up. The mean time taken for re-epithelization after surgery was 2.77 0.79 weeks. Although, there is always a possibility of graft dislocation as seen by Choudhary et. al which can be re-positioned and remains stable. Other observations which were similar to amniotic membrane were also seen with Bowman membrane after surgery. Most important was decrease in inflammation which was fast and was seen soon after surgery and the authors believe it to be a trophic effect. This also aided in transparency of healing cornea due to diminished fibroblast response. Second observation was the formation of a cyst below the membrane which lasted for two to three weeks and replaced with granulation tissue. Similar cysts were seen by other workers during amniotic membrane transplantation. It is probably due to secretions from the damaged cells below the membrane. Thirdly, epithelisation was quick enough and was aided by stem cells provided over it.

To document for the corneal thickness of the cornea we used anterior segment optical coherent tomography (AS OCT) which acted as a substantiating evidence that due to the scaffolding and support and the help it provided in the formation of granulation tissue of the bowman's membrane the corneal thickness increased the cornea healed and the visual acuity of the patients increased at the end of the study. In a few cases (n=5), there was a presence of hypopyon seen on first postoperative day which went away with time (about 2 weeks) and we believe it was reactionary to the double trauma and uveal inflammation.

The other benefits that need to be noted is the non-immunogenic nature of the bowman's membrane as it is acellular and the method of using therapeutic grade corneas for the treatment of patients that spares optical grade corneas to a more judicious use. Also, as the surgical method involved tuck-in of the graft and not suturing it saved the patient from suture related complications, saves surgical time, and reduces cost.

CONCLUSION

What we have seen is bowman's membrane is one solution for the many problems in the treatment of non-healing ulcer as it acts at various choke holds of the disease which none of the treatment has been able to provide us with. The membrane acts as a support for epithelial growth and scaffold for nerve growth is a very promising treatment in which the author believes is the perfect substitute for the treatment of non-healing ulcers. However, more number of cases needs to be done to prove this further.

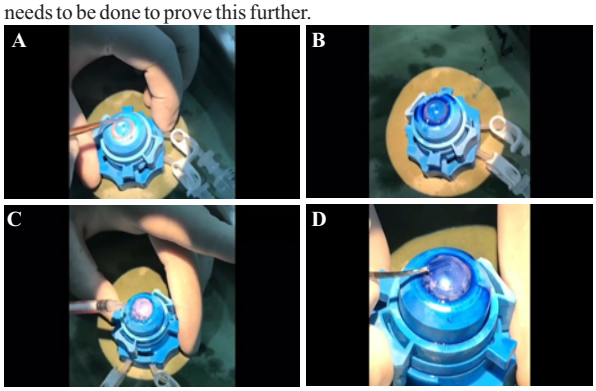

Figure 1: Surgical steps of harvesting Bowman's Lenticule: A-Scraping of epithelium, B-Staining of bowman's membrane with trypan blue dye, C-Creation of emphysema in anterior stroma, D-Separation of bowman's membrane,

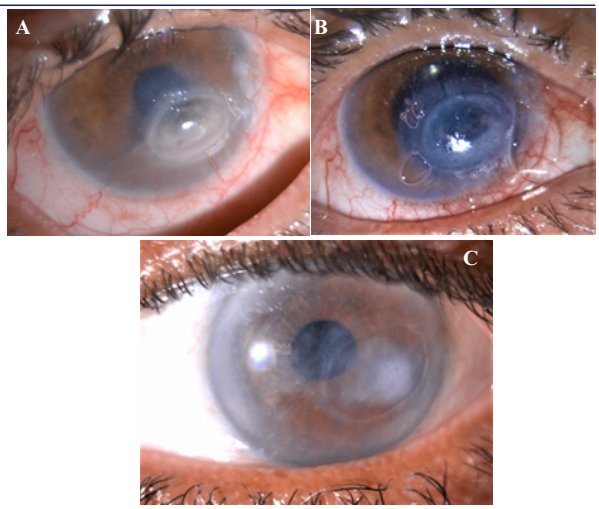

Figure 2 : A – Preoperative picture of resolved ulcer, B- Postoperative Day-1 with BCL, BM in place, C – 6 months Postoperative picture.

Conflict of Interest: None
Financial Support: Nil

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