Bowman's membrane lenticule tuck-in: A new approach for the management of neurotrophic ulcers

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Abstract:

PURPOSE: To evaluate a new surgical method for managing nonhealing neurotrophic ulcers using a novel technique of tucking-in Bowman's membrane lenticule in the ulcer defect.

METHODS: A total of 22 eyes of 22 patients with neurotrophic ulcers of various etiologies and stages were included and underwent a surgical process where a donor Bowman's membrane lenticule 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 primary outcomes measured were healing (stable epithelialization at 12 months) and best-corrected visual acuity (BCVA) improvement.

RESULTS: Twenty-two eyes of 22 patients with neurotrophic ulcers underwent Bowman's membrane lenticule tuck-in procedure. Complete re-epithelialization was achieved in 21 eyes (95.45%). The average healing time was 2.77 ± 0.79 weeks. The mean corneal thickness improved from 267.36 ± 94.56 mm preoperatively to 435.9 ± 47.71 mm at six months postoperatively. The mean BCVA also improved from 0.05 ± 0.07 preoperatively to 0.24 ± 0.24 postoperatively one year. One patient (4.54%) showed recurrence after one month, and the epithelial defect persisted till the end of the study.

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, neurotrophic ulcers, corneal transplantation, graft tuck-in, ulcer recess

Introduction

A breach in corneal epithelium along with surrounding stromal infiltration is known as a corneal ulcer, and healing is rapidly facilitated by epithelial cell proliferation leading to prompt re-epithelialization under normal circumstances. Sensory corneal innervation by ophthalmic division of the fifth nerve is supposed to play an important role in maintaining a healthy ocular surface. Corneal denervation causes decreased vitality, metabolism, and mitosis of epithelial cells with subsequent epithelial changes, including intracellular edema, loss of microvilli, and abnormal development of the basal lamina.[1,2]

Neurotrophic ulcers are a degenerative condition of the cornea where the loss of sensory innervation leads to recurrent epithelial breakdown and poor wound healing leading to persistent corneal ulceration. These are highly refractory to treat and are responsible for loss of vision, constant watering, pauses risk of infection, secondary glaucoma, endophthalmitis, panophthalmitis, autoevisceration, etc.[3]

Varieties of treatment options have been attempted ever since and improvised from time to time. Still, most of the techniques have a limited success rate due to the multifactorial nature of the disease. Medical therapy is given in the initial stages of the disease by discontinuing all the toxic topical medications and supplementation with preservative-free lubricants and autologous serum.[1,4] If the defect still persists, surgical procedures such as corneal gluing, bandage contact lens, conjunctival flap, tarsorrhaphy,

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amniotic membrane, and corneal transplantation can be opted.[5,6] Although the long-term outcomes of these procedures are unsatisfactory due to the recurrence of disease, the newer approach for the management of neurotrophic ulcers always has been a topic of research.[7] Various other factors, such as nerve growth factors, insulin-like growth factor type I, fibronectin, plasminogen activator, matrix metalloproteinase inhibitors, ascorbic acid, and substance P, are the other options being tried, but cost-effectiveness is a big concern.[4,8-11] A thin stromal lenticule, obtained as a by-product of the femtosecond SMILE procedure, is also claimed to have good results.[12,13]

In our study, the aim was to provide a cover to the bare ulcer area with a membrane that should be of good tensile strength yet comfortable, preferably natural and innate, and should provide a smooth and strong surface for the corneal epithelium to rapidly grow over it and fill the ulcer gap without producing any irregularities. Amniotic membrane was one such option, but it neither has tensile strength nor good thickness. On the contrary, the Bowman's membrane is the strongest layer of the cornea, has a natural and innate structure, and provides a very smooth surface for the epithelium to grow.[14,15] Furthermore, it can be secured in place by either gluing, suturing, or even tucked without help. Bowman's membrane transplantation has already been attempted to stabilize advanced keratoconus cases and perforated corneal ulcers with a reasonable success rate.[14,16,17]

Hence, we devised and developed a new surgical technique for neurotrophic ulcers by tucking Bowman's lenticule in the recess covering corneal ulcers and assessed its efficacy in nonhealing neurotrophic ulcers.

Methods

This hospital-based prospective, noncomparative type of interventional study was conducted between April 2017 to December 2019 on the patients admitted to the SMS Medical College and Attached Hospitals in northwest India.

After obtaining the institutional ethical committee approval and before commencing the study, each patient was explained the investigative nature of the study, the advantages, and potential risks. The surgical technique and its visual prognosis were adequately explained, and informed consent was taken.

Inclusion criteria

a. Ambulatory patients of either gender of all ages at the time of screening and who (or their guardian in case of minors) were capable of understanding the details of their disease, its management, and prognosis and giving written informed consent
b. Nonhealing noninfective corneal ulcer of neuropathic origin established by reduced or absent corneal sensitivity and not more than 4.50 mm size of more than 2 weeks.

Exclusion criteria

a. Patients who were bedridden, debilitated, or suffering from malignancy or on radiation/chemotherapy, etc., were not taken for study
b. Patients suffering from advanced ocular diseases such as advanced glaucoma and advanced retinal diseases
c. Patients who were not willing to complete workup or written consent
d. Patients with active infectious diseases such as TB and herpes zoster
e. Evidence of active infection in the concerned eye or the other eye
f. Allergy to fluorescein dye
g. Presence of high blood pressure of more than 150 systolic or ≥100 mmHg diastolic
h. Patients who were HIV, HBsAg, and HCV test positive
i. Females who were pregnant or breastfeeding

A total of 22 eyes of 22 patients with nonhealing ulcers due to damage of the 5th cranial nerve (part supplying to the cornea) and further confirmed by reduced or absent corneal sensations were included in the study. All cases failed to respond to medical management given according to etiology for at least 4 weeks and were sterile on microbiological examination.

All patients had undergone ophthalmological, systemic, and complete clinical evaluation, including best-corrected visual acuity (BCVA) in the decimal system and slit-lamp biomicroscopy.

The size of the corneal ulcer and epithelial defect was noted at its greatest dimension, along the two perpendicular axes. The depth of the ulcer was assessed by measuring the corneal thickness at the thinnest point, and the extent of corneal vascularization was also noted. Corneal sensations were checked using a thin, sterile cotton fiber. The same surgeon performed all surgeries. Bowman's lenticule was harvested from the donor cornea of therapeutic grade and procured from the certified eye bank.

Surgical technique

Under peribulbar anesthesia, debridement was carried out from the ulcer bed and surrounding tissue, removing all dead cells. A recess was then created circumferentially with the help of a crescent knife in the anterior one-third of the stroma inside the ulcer. The length of recesses depended on the location of the ulcer. For centrally located ulcers, a large recess of 8-9 mm length extending up to the periphery of the cornea was created, while in peripheral ulcers, a 2-3 mm length of recess was made, preferably avoiding the pupillary area. For harvesting Bowman's lenticule, donor cornea of therapeutic grades was used. In the sequence, the donor cornea was first mounted on an artificial chamber (disposable artificial chamber, Katena, USA), the epithelium was scraped, and an emphysema was then created in the stroma to separate it from the overlying Bowman's membrane. After staining the surface with trypan blue dye (Aurolab), a flap was raised by giving a superficial nick just below the Bowman's layer, and the membrane was stripped off in toto, along with some fibers of the anterior stroma. The Bowman's lenticule, thus prepared, was further inserted and

tucked in the recess covering the ulcer. Wrinkles of Bowman's membrane, if any, were removed, and a bandage contact lens was placed over the cornea before closing the eye [Figure 1].

Postoperative management consisted use of preservative-free moxifloxacin 0.5% eye drop QID, carboxymethyl cellulose 1% eye drop QID, atropine 1% eye drop BD, and a short course of oral steroids starting with prednisolone 1 mg/kg for one week and tapered over 4 weeks. Topical steroids were given after the epithelialization of ulcer was completed and continued for 2 months. Follow-up was done postoperatively on 1 day, 1 week, 2 weeks, 4 weeks, and monthly, till 1 year, and BCVA, corneal thickness, and any other complications were recorded for each follow-up. Epithelium healing was checked with the help of fluorescein dye staining on a slit lamp every visit, and the time taken for epithelialization after surgery was noted in weeks. The bandage contact lens was removed after 1 month. For the study, re-epithelialization time, improvement in BCVA, and corneal thickness were measured as primary outcomes, and complete epithelialization of the ulcer, evident by negative fluorescein staining with no recurrences up to 12 months, was considered as a surgical success.

Statistical analysis

Statistical analysis was done using IBM Statistical Program for Social Sciences IBM® SPSS® Statistics V22.0 (SPSS Inc., Chicago Illinois, USA). Quantitative data were represented as mean ± standard deviation while qualitative data were expressed as a percentage. Paired *t*-test was used for comparing preoperative and postoperative quantitative data. $P < 0.005$ was considered statistically significant.

Results

A total of 22 eyes of 22 patients (17 males and 5 females) of nonhealing neurotrophic ulcers were included in the study. Our study's most common cause of nerve damage was viral, mostly old herpetic infections suggested by a history of recurrent ocular inflammations and corneal stromal haze suggesting stromal keratitis episodes. The total of cases in this subcategory was thirteen. Other group of cause of neurotrophic ulcers were mixed and could not be traced to exact causes, but long-standing non healing ulcerations together with a decreased corneal sensitivity was a constant finding. The total number of such cases was nine.

The mean age of patients was 56.40 ± 14.22 years and 77% of patients were male, while 23% were female. All patients underwent Bowman's membrane lenticule grafting, and surgery was uneventful in all cases. Although, one patient (4.54%) showed graft dislocation on 1st postoperative day, which was repositioned same day.

The mean ulcer size in the greatest dimension in two perpendicular axes was 3.5 (x 2.9) ± 0.69 millimeters and the mean time taken for re-epithelialization after surgery was 2.77 ± 0.79 weeks. However, one patient (4.54%) showed recurrence after 1 month, and the epithelial defect persisted till the end of the study.

The mean corneal thickness was 267.36 ± 94.56 mm preoperatively with 22.72%, 59.09%, and 18.18% of ulcers being superficial, moderate depth, and deep ulcers, respectively, which further increased to 435.9 ± 47.71 mm at 6 months postoperatively. This difference was considered statistically significant ($P < 0.0001$). The mean BCVA also improved preoperatively from 0.05 ± 0.07 to 0.24 ± 0.24 at postoperatively 6 months, and this difference was statistically significant ($P < 0.0005$) [Table 1 and Figure 2]. Figure 3 shows the representative image of anterior segment optical coherence tomography.

Discussion

The cornea is richly innervated by the third (ophthalmic)

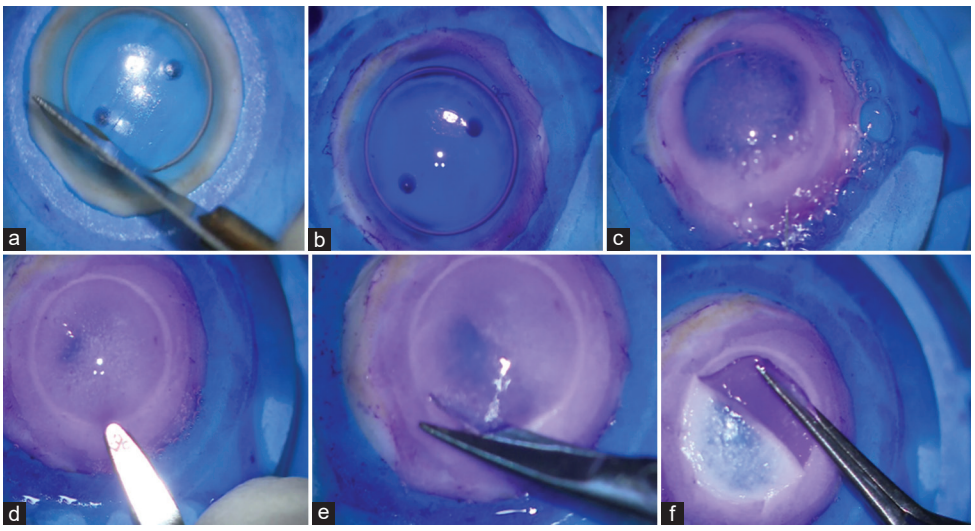

Figure 1: Surgical steps of harvesting Bowman's lenticule: (a) scraping of epithelium, (b) staining of Bowman's membrane with trypan blue dye, (c) creation of emphysema in the anterior stroma, (d) separation of Bowman's membrane, (e) raising flap of Bowman's membrane, and (f) stripping of lenticule in toto

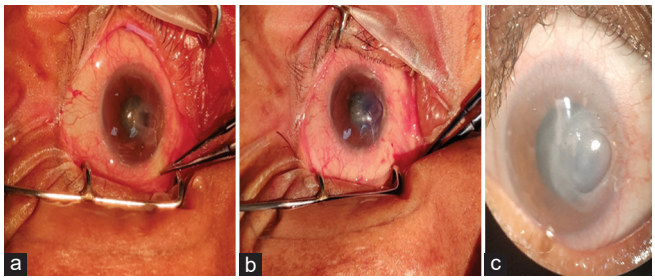

Figure 2: Neurotrophic ulcer healing and re-epithelialization at 6 months, (a) preoperative photograph, ulceration. (b) Postoperative photograph showing stained Bowman's lenticule and contact lens placed over the cornea and (c) postoperative photograph at 6 months marking shows Bowman's membrane lenticule inserted

Table 1: Demographic and clinical data of patients

	Preoperative	Postoperative	*P*
Mean age (SD) years	56.4±13.87		
Male to female ratio	3.4:1		
Mean epithelial defect (mm×mm)	3.5×2.9±0.69		
Mean epithelialization time (weeks)	2.77±0.79		
Mean corneal thickness (mm)	267.36±94.56	435.9±47.71	<0.0001
Mean BCVA	0.05±0.07	0.24±0.24	<0.0005

SD: Standard deviation, BCVA: Best-corrected visual acuity

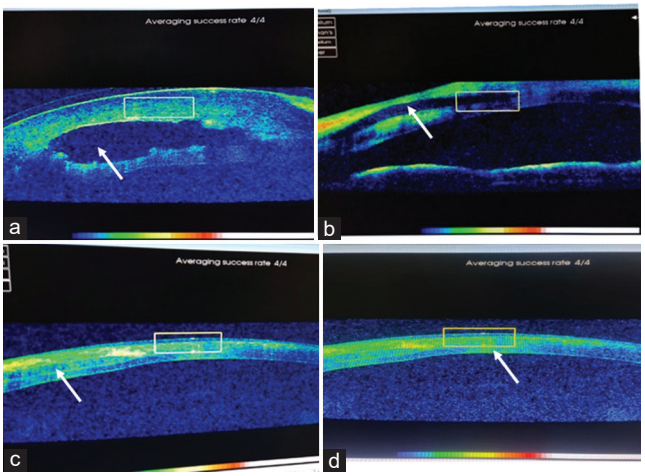

Figure 3: Anterior segment OCT (ASOCT) pictures of a case through timeline postoperative 2 weeks (a), 4 weeks (b), 6 weeks (c), and 6 months (d). (a) A cyst (arrow) formation below the Bowman's membrane lenticule filled with inflammatory cells and granulation tissues. (b) Absorbing fluid and organizing granulation tissue. (c) Almost complete absorption of fluid. (d) The complete merging of the two tissues. OCT: Optical coherence tomography

division of the fifth (trigeminal) nerve and autonomic nerves. Nerve bundles enter the cornea in the limbus deeply and move deeper to the center, below the anterior third of the stroma, penetrating Bowman's layer, while they move superficially and create a dense nerve fiber network between Bowman's layer and basal epithelial cells responsible for brisk corneal reflex. Any interruption in the sensory supply results in neurotrophic ulcer[3] and is characterized by reduced corneal sensations, recurrent epithelial breakdowns, and impaired healing leading to persistent epithelial defects.[1,10] These ulcers are refractory to treat and manage, depending on the underlying cause, condition of the epithelium at the initial presentation, and the depth of the ulcer. Treatment modalities described so far include patching, scleral contact lens, cyanoacrylate glue, conjunctival flap, amniotic membrane transplantation (AMT), and tarsorrhaphy.[18] Among all, AMT is most successful method.[19] Khokhar *et al*.[20] reported 73.33% success rate of AMT in neurotrophic cases, while the success rate reported by Chen *et al*.[6] is 76.4%. The lower success rate of AMT is due to the delicate nature of membrane, the basic problem of local neurological deficit, and high recurrences. Most patients later require some kind of corneal transplantation once or more. Thus, the need of the hour for the management of neurotrophic ulcers is to provide a stronger support that allows epithelium to regrow and holds it for a longer time, hence giving an opportunity for local neural regeneration.

In this study, we provided a strong Bowman's lenticule support to the ulcer, which is a true innate layer of cornea. Our Bowman's lenticule is 30 to 40 μm thick acellular membrane, providing integrity and mechanical strength to the cornea. van Dijk *et al*.[21] have described the role of midstromal Bowman's layer transplantation in the management of advanced keratoconus. In these cases, the Bowman's layer transplant restored the shape and tensile strength of the cornea and thus delayed the progression of keratoconus and keratoplasty.

In our study, the Bowman's lenticule was prepared from the donor cornea of therapeutic grade and was tucked in the anterior stroma, providing a natural smooth basement membrane for epithelium to grow and holding the grip for longer. Our experience with this kind of ulcers (which was practically mostly postherpetic neuropathic) was that it needed a strong and stable basement membrane that can last indefinitely for the epithelium to grow and stabilize (i.e., growing into normal 7–8 cell layers) together with at least some neural elements. Bowman's membrane or layer subserved these important properties. Firstly, it provides a very strong base for epithelial maturation and stays there indefinitely, secondly, normally Bowman's layer in cornea provides a microenvironment for nerve plexus formation, which is fulfilled here. Bowman's membrane also reduces inflammation below it which also helps in nerve regeneration. Our results of stable epithelialization suggest some nervous regeneration.

Twenty-two eyes of 22 patients with nonhealing neurotrophic ulcers underwent Bowman's lenticule grafting. The procedure was successful in 95.45% of cases who remained healed until the last follow-up. The mean time taken for re-epithelization after surgery was 2.77 ± 0.79 weeks. Similar results were seen in a study by Choudhary and Agrawal,[14] where epithelialization of the wound after BMT in cases of small corneal perforation was completed over 2 weeks, suggesting the role of the Bowman's membrane in epithelial healing. Graft

dislocation on the 1st postoperative day was seen in one patient who became stable after repositioning. Recurrence was also noted in one patient with recurrent herpetic keratitis.

Corneal thickness at the thinnest point was measured with anterior segment optical coherent tomography, and ulcers were classified as superficial, moderate depth, and deep ulcers accordingly. At the end of the study, corneal thickness improved in all patients, proposing that Bowman's membrane can act as scaffolding for epithelial repair and allows granulation tissue to grow between the host stroma and Bowman's graft, increasing the thickness irrespective of preoperative ulcer depth. This also led to significant improvement in BCVA at the end of the study.

Since Bowman's membrane is a tough acellular, relatively avascular, and nonantigenic structure lying between the host epithelium and host stroma, the risk of graft rejection is very well precluded. None of the patients presented with the signs of graft rejection in our study. It exerts a trophic effect by providing constant support, on which epithelium can grow, and thus helps in reducing ocular surface inflammation. Furthermore, it is harvested from therapeutic-grade corneas, and optical corneas can be saved for other purposes. Furthermore, as surgery was suture-less, it eliminated suture-related/glue-related complications and making it less time-consuming.[21]

There were several limitations in our study, including the small sample size and the follow-up period of being only 1 year which was short to assess the long-term effect of Bowman's membrane in the management of neurotrophic ulcers and the recurrence rate. However, meta-analysis with similar studies was done, but there was no control group to compare the results in the study itself. Larger, prospective, randomized controlled trials should be further investigated with longer follow-up period to fully establish the difference in the outcome.

Conclusion

Thus, the authors believe that for reasonable nerve regeneration, a stable and strong base is required for a longer duration for the epithelium to regrow. Since the nerve plexus is located in and around the Bowman's layer, it is the perfect substitute for the surgical management of neurotrophic ulcers.

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Conflicts of interest

There are no conflicts of interest.

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