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A new surgical technique for the management of Peripheral Ulcerative keratitis using Bowman's Membrane Lenticule.

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Abstract
Purpose: *To evaluate a new surgical technique for the management of peripheral ulcerative keratitisby tucking-in of bowman's membrane lenticule over the ulcer defect.*
Methodology: *A total of 11 eyes of 11 patients with peripheral ulcerative keratitis were treated surgically where a donor bowman's membrane was harvested resembling the contours of the ulcer and after making a recess in the anterior one-third of stroma all around 360 degrees was tucked underneath ulcer edges. Healing (stable epithelization at 6 months) and improvement in best-corrected visual acuity (BCVA) were taken as the primary outcomes.*
Results:*Total eleven patients were enrolled, seven males (64.30%) and four females (34.30%) with age ranging between 45 years to 85 years. The mean age being 64.090 ± 13.0555 years. Mean epithelizationtime in weeks was 2.181818 ± 0.7158 weeks andthe mean ulcer size was 3.7 × 2.5 + 1.06.*
The preoperative mean BCVA was 0.2422 + 0.1382 decimal units and the postoperative was 0.554 + 0.2133 which suggest extremely good and prognostically determinable results (P value <0.0001).
Mean preoperativeCorneal thickness value was 240.4545 + 79.619 microns and the postoperative value was 416.4545 + 50.420 microns which was significantly better (P< 0.0029).
Conclusion:*The study establishes the safety and efficacy of donor bowman's membrane lenticule tuck-in inthe treatment of peripheral ulcerative keratitis requiring minimal instruments and expertise.*
Keywords: *Bowman's membrane lenticule, peripheral ulcerative keratitis, Corneal transplantation, Graft tuck-in, recess*

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I. Introduction

Peripheral ulcerative keratitis refers to a crescent-shaped destructive inflammation of the juxtalimbal conjunctiva and corneal stroma associated with an epithelial defect, presence of stromal inflammatory cells, and stromal degradation [1].The hallmark features of epithelial defects and stromal destruction is formation of gutter which may increase in dimensions and depth (even perforate), as a result of a complex interplay of factors including host autoimmunity and the peculiar anatomic and physiologic features of the peripheral cornea and environmental factors[2].

Although the exact pathophysiological mechanisms of peripheral ulcerative keratitis are unclear, circulating immune complex deposition, autoimmune reactions to corneal antigens and hypersensitivity reactions to exogenous antigens have been proposed, with evidence suggesting that both humoral and cell-mediated mechanisms (T cell and B cell) are involved[3][4]. Unlike the avascular central cornea, the peripheral cornea is closer to the limbal conjunctiva and derives part of its nutrient supply from the limbal capillary arcade, a source of immunocompetent cells, e.g., macrophages, Langerhans' cells, lymphocytes, and plasma cells[5].

Numerous treatment modalities have been tried with a mix of medical and surgical therapies that aim to curtail the damage caused by the mounting immune response and to provide the patient with the best possible outcome but due to the immensity of the immune response and resistance to treatment, presentmanagementshave been short of success. The treatment algorithm is very straightforward, starting with topical steroids then moving on to systemic steroids and immunomodulatory drugs and finally surgical treatment by conjunctival resection, cyanoacrylate glue, amniotic membrane grafts, and finally corneal patch grafts[6].

Although, long-term outcomes of these procedures are unsatisfactory and unpredictable due to recurrence of disease, the newer approaches for the management of such ulcers always need to be researched for.

We, in our study have developed a new surgical modality by filling the gutters or larger defects, by a piece of Bowman membrane lenticule which is very strong, transparent, acellular innate structure (in comparison to amniotic membrane). Till now,it hasbeen attempted for stabilization in advanced keratoconus cases[7][8] and also in perforated corneal ulcers[9].

II. Methodology

The study is a hospital-based prospective, non-comparative type of interventional study which was conducted between 2018 to 2020on the patients admitted in a tertiary care (medical college) centre of Rajasthan, India.The study was started after obtaining approval from theinstitutional ethical committee, and the study was carried out under the tenets of the Declaration of Helsinki. The patients wereexplained about the surgical and investigative nature of the study, the advantages, and the potential risk-benefit ratio followed by a well-informed and written consent in the patients' language only after that the patient was enrolled for the study. A total of 11 eyes of 11patients of peripheral ulcerative keratitis with non- healing ulcers (known as gutters)who did not respond to medical management for at least two weeks and only after any infectious cause of the lesion was ruled out i.e., negative on microbiological examination.

Patients who had a non-infectious non-healing lesion without perforation or thinning not greater than 4 mm in width (but the length could be anything) with visual acuity greater than perception of light, and ready for regular follow-ups were enrolled for the study. And those less than 18 years of age or greater than 85 years of age, showing signs of herpetic eye disease, history of corneal transplantation,patients not willing for surgery, and those who were not able to come on follow up, were excluded from the study.All patients had undergone ophthalmological, systemic, and full clinical evaluation including best-corrected visual acuity (BCVA) in the decimal system and slit-lamp bio-microscopy. The size of the corneal ulcer and epithelial defect was noted at its greatest dimension, along the two perpendicular axes. Depth of the ulcer was assessed by measuring the corneal thickness at the thinnest point and the extent of corneal vascularization was also noted. A sterile cotton fibre was used to check corneal sensations. All surgeries were performed by the same surgeon. Bowman's lenticule was harvested from the donor cornea of therapeutic grade, procured from the certified eye bank.

Surgical technique

Bowman membrane harvesting:

Donor cornea (cornea of therapeutic grades were used) received from eye bank was mounted on a disposable artificial chamber (Katena, USA). The epithelium was debrided using a number 15 blade by gentle scraping. The underlying bowman's membrane was stained with trypan blue dye (Sunways). Stromal emphysema was created by injecting air into the anterior stroma with the help of an insulin syringe. This helps separate the underlying bowman's membrane from the stroma. A suitable sized trephine was used (usually 8-9 millimeters) to groovebowmans membrane with gentle pressure. The grooved membrane is grasped with toothed forceps and with the help of a crescent blade (Webbel edge) the bowman's membrane is gently and slowly separated. After initiation with the help of a crescent blade rest of the separation is done with the help of an iris repositor (blunt dissection). The rest of the bowman's membrane is stripped by holding it with the help of plain forceps.

Bowman membrane grafting:

Under peribulbar anaesthesia, the ulcer base is scrapped gently to remove any debris or any underlying loose tissue. With the help of a crescent blade, a recess was then created circumferentially, in anterior one-third of stroma and in sclera on opposite sideinside the ulcer. The bowman'slenticule was trimmed to the appropriate size (a little bigger than the size of the ulcer margins, so as to tuck the graft underneath the ulcer edges) and was further inserted and tucked in the recess covering the ulcer. Wrinkles of the bowman's membrane, if any, were removed and a bandage contact lens was placed over the cornea before closing the eye.

Postoperative treatment and evaluation:

Postoperative management consisted of use of eye drop Moxifloxacin 0.5% (preservative- free) QID, eye drop Carboxymethyl Cellulose 1% QID, eye drop Atropine 1% BD, and a short course of oral steroids starting with Prednisolone 1 mg/kg for one week and then tapered over 4 weeks. Topical steroids were given after the epithelization of the ulcer was completed and continued for 2 months. The patient was examined on the first postoperative day on a slit lamp. Then follow up visits were planned on 1 week, 2 weeks, 4 weeks, and monthly, till 6 months. On each visit slit lamp examination, visual acuity, corneal thickness, anterior segment optical coherence tomography, fluorescein staining,and any othercomplications were recordedto check for the progression of healing after treatment.Bandage contact lens was removed after 1 month. For the purpose of the

study, success was considered when the ulcer healed with no rejection indicated by complete epithelization of the ulcer(evident by negative fluorescein staining) and with no recurrences up to 6 months.

Statistical analysis

The compilation of results was done on a proforma designed in a Microsoft excel spread sheet (Microsoft, Redmont, WA). The entries were rechecked for human error while typing. Statistics for windows version 22.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The qualitative data were recorded as percentages whereas quantitative data were represented as mean ± standard deviation. Paired t-test was used for comparing preoperative and postoperativequantitative data. P value of <0.005 was considered for the significance of the results.

III. Results

There were total eleven patients enrolled with seven males (64.30%) and four females (36.60%) with mostly elderlies (age ranging between 45 years to 85 years). The mean age and standard deviation being 64.090 ± 13.0555 years. The epithelization time in this group was extremely fast probably because of thinner and longer gutters and the mean time in weeks was 2.181818 ± 0.7158 weeks. Localized inflammation and dryness was hallmark of this group and therefore severe proven systemic diseases were taken as comorbid condition. Five (45.45%) eyes had comorbidity in the form of advanced Rheumatoid arthritis but it did not affect the healing or the visual outcome. The mean ulcer size was 3.7 × 2.5± 1.06 mm suggesting thinner and longer gutters.

Visual performance was most impressive as it involved peripheral part of corneas and the preoperative mean BCVA was 0.2422 ± 0.1382 decimal units and the postoperative was 0.554 ± 0.2133 which suggest extremely good and prognostically determinable results (P value <0.0001).

Corneal thickness was improved to almost near normal levels and contour although pantacam was suggestive of a thinned cornea in periphery. Mean preoperative value was 240.4545 ± 79.619 microns and the postoperative value was 416.4545 ± 50.420microns which was significantly better (P< 0.0029).

IV. Discussion

Peripheral ulcerative keratitis has a disease pattern unique to its own due to the peculiar features of the peripheralcornea. The peripheral corneahas distinct morphologic and immunologic characteristics due to proximity of conjunctival vasculature, which provides access for circulating immune complexes via the capillary network. Deposition of immune complexes in the terminal ends of limbal vessels initiates immune-mediated vasculitis, and causes inflammatory cell and protein leakage due to vessel wall damage[10].

The very fact that this disease arises due to self-destruction by the immune system makes it much more difficult to treat and making it liable to recurrences even after treatment. The current treatment strategy for PUK with underlying systemic disease in initial stage is systemic corticosteroids plus a cytotoxic agent during the acute phase of the disease. The exact cytotoxic agent may differ according to the underlying systemic disease[11][12][13][14].

But as the disease progresses the peripheral cornea is eroded by the inflammatory destruction (gutter formation) and if the gutter progresses, surgical management is to be opted. Surgical modalities described so far, include patching, scleral contact lens, cyanoacrylate glue, conjunctival flap, amniotic membrane transplantation and tarsorrhaphy. Amniotic membrane transplantation shows promise when compared to the others and is the most successful and acceptable of all but its short-coming being that it is a delicate membrane and thus fails to provide structural support in a thinned-out cornea affected by peripheral ulcerative keratitis. All of this leads to recurrences which are very commonin most of the patients who later require some kind of corneal transplantation.

Here is when bowman membrane stands as the harbinger of a good potential treatment option, which is a true innate acellular layer of the cornea and provides support or scaffold for the epithelisation of cornea and nerve growth which helps in the healing of the cornea. Additionally, it also provides tectonic support to the thinned-out cornea.

Van Dijk et.al[7][8] in their study observed that bowman layer prevented ectasia and provided the cornea with shape and tensile strength thus delaying progression in case of keratoconus and keratoplasty.

In our study 11 eyes of 11 patients of peripheral ulcerative keratitis underwent bowman's lenticulegraftingwith a high percentage ofsuccess. The mean time taken for re-epithelization after surgery was 2.18 ±0.71weeks. These results show concordance with a study done by Choudhary et. al[9]who reported epithelization within 2 weeks in the setting of small corneal perforation (less than 4 millimeters) being surgically treated by bowman membrane tuck in in emergency setting.

As corneal thinning is another problem faced post medical treatment of with other surgical modalities it was noted by us that on serial anterior segment optical coherent tomography (AS OCT) imaging the thickness of the cornea improved for all patients thus hypothesising the possibility of bowman's membrane providing a scaffold for the epithelial to grow and the nerve plexus to regenerate thus providing a duality in its usefulness in treating cases of peripheral ulcerative keratitis.

Furthermore, it is noteworthy that being an avascular itis a non-antigenic (or least antigenic as none of the workers so far has encountered rejection or reaction episode) structure and thuschances of graft rejection are precluded. The corneas used for the intervention are therapeutic grade corneas which help us save the optical corneas for other purposes. Also the technique is a suture less one which helps us save time and the tucking in process being a relatively easy one requires less expertise in-turn leading to lesser complications.
However, a study with larger sample size with a longer follow up time could have been more informative.

V. Conclusion

The fact that bowman's membrane is a strong layer that provides a scaffold to the growing epithelium and the regenerating nerves along with tectonic support provided to the thinned out cornea makes it near ideal for healing of peripheral ulcerative keratitis and all these properties make the author believe in the future potential of the bowman's membrane.

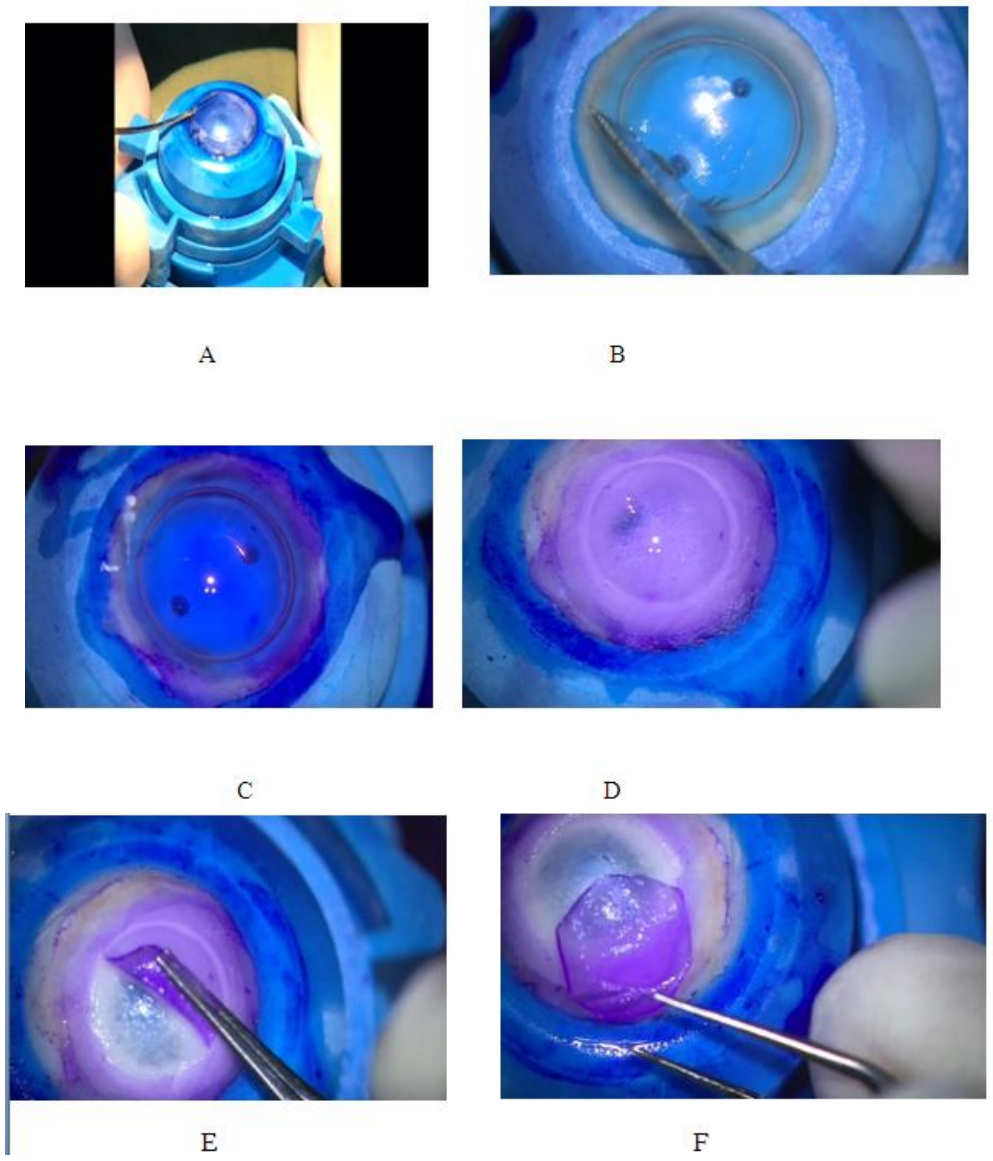

Figure 1: Surgical steps of harvesting Bowman's Lenticule: A- Artificial chamber with Corneal button mounted, B- Epithelial debridement with trypan blue dye, C- Marking with trephine, D-Creation of emphysema in anterior stroma, E-Stripping of lenticule in toto, F – BM lenticule after separation.

A B

Figure 2 : A – Preoperative PUK showing gutter, B- Postoperative picture showing gutter filled with transparent BM lenticule.

Table 1 showing demographic and clinical data of patients.

	Pre-operative	Post-operative	P value
Mean Age (years)	64.090 ± 13.0555		
Male to Female ratio	6.4:36		
Mean Epithelial Defect (mm*mm)	3.7 × 2.5± 1.06		
Mean Epithelization time (weeks)	2.181818 ± 0.7158		
Mean Corneal Thickness (mm)	240.4545+79.619	416.4545+50.420	< 0.0029
Mean Best Corrected Visual Acuity	0.2422 ± 0.1382	0.554 ± 0.2133	< 0.0001

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