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REVIEW ARTICLE

Revolutionizing vision restoration: Unleashing the power of Bowman's layer transplantation

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Abstract

Bowman layer inlay and outlay transplantation is a cutting-edge surgical technique that has revolutionized the field of corneal transplantation. This novel technique entails the transfer of the Bowman layer, a slender layer of the cornea, with the purpose of rectifying diverse corneal abnormalities and enhancing visual results. The Bowman layer inlay and outward transplantation approach differs from typical corneal transplantation methods by specifically targeting and replacing the affected layer of the cornea, rather than replacing the whole cornea. This method has many benefits, including accelerated healing periods, less chance of rejection, and enhanced visual acuity. Bowman layer inlay and outlay transplanting is recommended for several corneal diseases and illnesses. Common indications for this operation include keratoconus, corneal dystrophies, corneal scarring, corneal ectasia, and corneal abnormalities. This article will examine the complexities of Bowman layer inlay and outward transplanting, its uses, and the possible advantages it provides to individuals with corneal diseases. Bowman layer inlay and outlay transplanting appropriateness for each unique instance is evaluated by a comprehensive review of the patient's particular condition and demands.

Keywords: Bowman's layer inlay transplantation; Bowman's layer onlay transplantation; Keratoconus.

Why do we Need Bowman's Layer Surgery?

Anatomical considerations

Bowman's layer (BL) is a narrow stratum inside the cornea, between the corneal epithelium and the stroma. The composition of the structure is comprised of collagen fibrils that are arranged randomly. The collagen fibrils in the anterior stroma adhere to Bowman's layer. The thickness of the material is about 12 µm and consists of a disordered configuration of collagen fibrils, mainly composed of types I and III, together with proteoglycans.[1] The diameter of these fibrils ranges from 20 to 30 nanometers. The BL has an average radius of 7.34 mm and experiences a reduction in thickness as an individual ages.[2] The surgical intervention known as "Bowman's layer transplantation" (BLT) has been used to treat progressive keratoconus (KC). The primary objective is to mitigate and establish stability in cases of corneal ectasia, resulting in enhanced visual results and a steady cornea condition.

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In the first KC stages, individuals often use rigid contact lenses to provide a consistent anterior optical surface. However, as the disease progresses, contact lens intolerance becomes more prevalent, necessitating the consideration of surgical interventions such as penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK). Since 2003, there has been an emergence of UV-A-induced collagen cross-linking as a viable therapeutic option for KC patients with corneas that have a minimum thickness of 400 µm and a preoperative maximal keratometry (Kmax) measurement of 58 diopters (D) or less. Advancements in technology have facilitated the treatment of corneas that are both thinner and steeper. However, the management of cases with advanced KC may be restricted to either PK or DALK. These procedures can be complicated by issues related to sutures, abnormalities in epithelial wound healing, and changes in corneal curvature caused by the progression of KC in the surrounding cornea. As a consequence, a series of secondary complications may arise, leading to unsatisfactory visual results.[3]

A major advantage of BLT is its potential to reduce and stabilize corneal ectasia in advanced KC.[4] The transplantation of the Bowman's layer can provide long-term stabilization of ectasia. The procedure aims to strengthen the cornea and improve its shape, leading to improved visual outcomes and corneal stability. The primary objectives of the BLT procedure are to maintain functional visual acuity, preserve the patient's corneal tissue, and perhaps postpone or circumvent the need for more invasive operations like PK or DALK, all while minimizing the likelihood of post-operative problems. The aforementioned effects have been shown to exhibit stability, with no statistically significant variations seen throughout the 6–18 months' follow-up period.[5]

The implantation of a Bowman layer graft results in corneal flattening through the anterior surface traction, leading to a direct reduction in spherical aberration.[6] The result of intracorneal ring-segment implantation also exhibits similar phenomenon, albeit the danger of migration and interface reactivity is much reduced with the use of BLT. This phenomenon may be attributed to the comparable mechanical properties shown by this tissue in relation to the adjacent corneal stroma. Moreover, the potential for allograft rejection is deemed low due to the absence of cellular components in the Bowman layer, which mostly comprises collagen fibers. The enhancement of contact lens tolerance is seen in cases with advanced KC (with an estimated corneal flattening of 8 D).[7]

Steps in BL transplantation surgery

Donor tissue preparation

According to the Amnitrans EyeBank in Rotterdam,[8] Bowman's layer grafts are obtained directly from donor spheres (technique-I) or previously excised corneoscleral buttons (technique-II) (Fig. 1).

For technique I, donor globes obtained <24 h postmortem are mounted on a custom-made holder with a suction cup. After all corneal epithelium was removed using surgical spears; a superficial incision is made over 360° just within the limbal corneal periphery using a 30-gauge needle. With a single tip of a McPherson forceps (Moria, Medical Workshop, Groningen, the Netherlands), the peripheral edge of BL (where the tissue had been scored) is lifted from the underlying anterior stroma. By grasping the edge with the McPherson forceps or custom-made forceps with rounded edges (DORC International, Zuidland, the Netherlands), the entire BL is carefully peeled away by gentle slow movements to free the tissue from its underlying attachments.

For technique II, from whole globes enucleated <24 h postmortem, corneoscleral rims are excised, and the endothelium was evaluated as previously described. Subsequently, the corneoscleral rims are stored by organ culture in a modified minimal essential medium (CorneaMax; Eurobio, France) at 31°C until graft preparation. If the tissue was deemed suitable for descemet membrane endothelial keratoplasty (DMEK), before the BL preparation a DMEK graft is prepared, is again kept in the culture medium un-

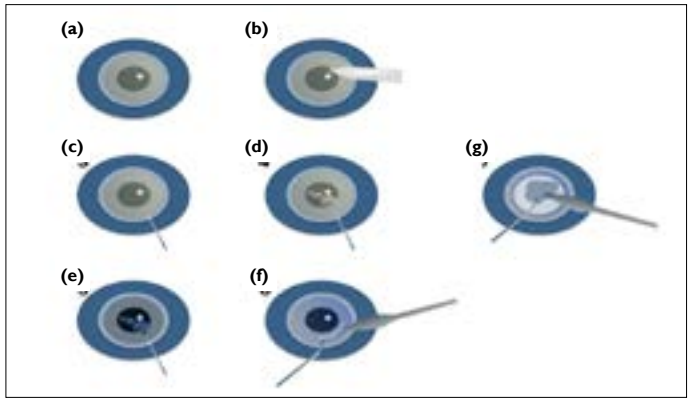


Fig. 1. Bowman's layer donor tissue preparation (All draftsmanship was provided by industrial designer Elif Oykü Karataş). **(a-b)** Air is used to create an artificial anterior chamber onto which a donor cornea with a scleral rim may be placed. **(c-d)** The stroma was delineated from the Bowman membrane by injecting air. **(e-f)** The Bowman layer was then identified by staining with trypan blue. A 360 scoring was done with a bent 30-gauge needle to delineate the Bowman membrane. **(g)** Using a crescent blade and fine-toothed forceps, the Bowman membrane was gently separated from the underlying stroma.

til BL preparation. At the time of BL preparation, the corneoscleral rim (with or without its descemet membrane and endothelium) is placed on an artificial anterior chamber (Katena; Rockmed, Oirschot, the Netherlands; Network Medical, Ripon, United Kingdom; or Gebauer Medizintechnik, Neuhausen, Germany), epithelial side up with the artificial anterior chamber filled with saline and subsequently debrided of its epithelium. Thereafter, scoring and isolating the BL graft from the underlying stroma are executed as described in technique I.

With both techniques, after finishing the preparation, each BL is evaluated by light microscopy and trephined if required. Because of the inherent elasticity of the tissue, BL grafts spontaneously curled into a single or double roll with the epithelial border at the outside. The BL roll is submerged in 70% ethanol to remove any remaining epithelial cells and again stored in the organ culture medium until the time of transplantation.

Recently femtosecond laser is being investigated for harvesting the donor BL. Initial, feasibility analysis has shown the creation of a thick but relatively smooth posterior cut edge in the femtosecond laser group, versus a virtually isolated BL with irregular rests of dispersed stroma in the manually dissected group.[9]

BLIT surgical technique

Surgery is started after administering local anesthesia, ocular massage, and a Honan balloon for 10 min, with positioned in the anti-Trendelenburg position. In short, at the 12-o'clock position, 1–2 mm outside the limbus, a 5-mm superficial scleral frown is made. After filling the anterior chamber completely with air, a corneal pocket is manually dissected over 360° up to the limbus, at an aimed mid-stromal depth, using the Melles spatula set (DORC International). As manual dissection in far advanced ectatic corneas may be challenging, the use of an intraoperative anterior segment optical coherence tomography (AS-OCT) fitted to an operating microscope has been evaluated to aid visualizing the dissection plane.[10] However, the costs–benefits of this technology should be considered.

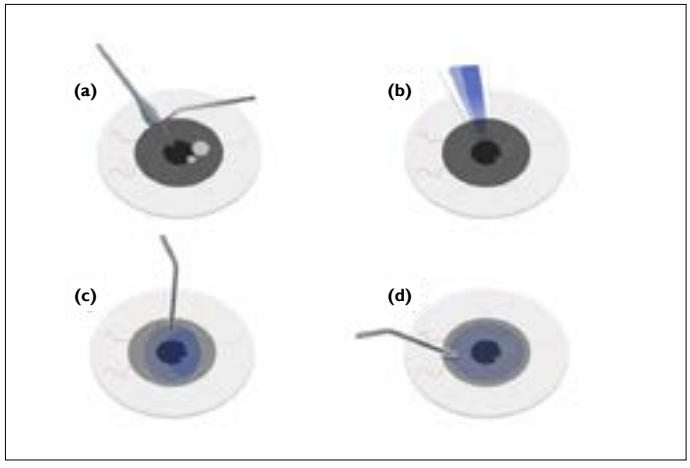


Fig. 2. Bowman's layer inlay transplantation (Elif Öykü Karataş, industrial designer). **(a)** Corneoscleral tunnel was done superiorly/temporally, and the same tunnel was extended throughout the cornea from limbus to limbus, 360° within the recipient cornea at midstromal level with the help of regular crescent blades and lamellar dissectors. **(b)** The harvested Bowman layer was then inserted into the stromal pocket with the help of a lens glide. **(c,d)** Any folds in the layer were ironed out with a spatula.

Into the created pocket, a glide (BD Visitec Surgical Glide [Fichman]; Beaver-Visitec International, Waltham, MA) is inserted, and air is removed from the anterior chamber.[3] Also, the intrastromal pocket could be created in the patient's cornea using a femtosecond laser machine (FS200, Wavelight).[11] The BL graft is again submerged in 70% ethanol for 30 s to remove all remnant cells, thoroughly rinsed with balanced salt solution (BSS; Bausch and Lomb, Rochester, NY), and stained with trypan blue (VisionBlue; DORC International). Then, it is placed atop the glide and slid carefully into the stromal pocket, unfolded, and centered using a cannula and BSS. Furthermore, it has been reported that the inlay could be injected into the stromal pocket using an intraocular lens injector, and its unfolding could be achieved using surface taps and manipulation with a 26-gauge cannula in the pocket.[11] At the end of the procedure, the eye is brought to normal intraocular pressure by filling the anterior chamber with balanced salt solution (Fig. 2).

BLOT surgical technique

In BLOT operation, first, the recipient corneal epithelium is debrided. If anterior stromal scarring is present, it is carefully further manually scraped. The stromal bed is then thoroughly irrigated with BSS to remove any epithelial remnants. An isolated BL graft, 8.5–9.5mm in diameter is stained with 0.06% trypan blue (VisionBlue; DORC International), and is simply positioned onto the anterior corneal stroma of the recipient eye and allowed to "dry in." This drying may "stick" the BL graft onto the surface of the recipient cornea, allowing it to be fixated without sutures or glue. Immediately postoperatively, a bandage contact lens may be applied to prevent the onlay graft from being dislodged; after 1 week, the graft may be completely re-epithelialized, and the contact lens removed (Fig. 3).[12,13]

A representative cross-sectional view of Bowman's layer transplantation is summarized in Figure 4.

Fig. 3. Bowman's layer onlay transplantation (Elif Öykü Karataş, industrial designer). **(a)** Careful mechanical scraping removes the epithelium. **(b)** Bowman layer lenticule is layed on the stroma. **(c)** With therapeutic contact lens covering, Bowman's layer is protected and epithelialization is achieved.

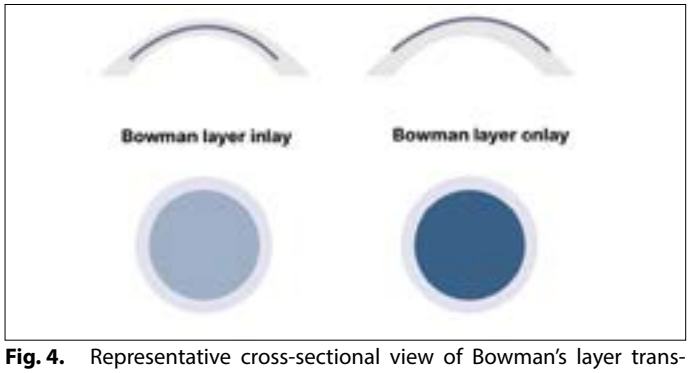


Fig. 4. Representative cross-sectional view of Bowman's layer transplantation (Elif Öykü Karataş, industrial designer).

Indications of BL Transplantation

1. Keratoconus

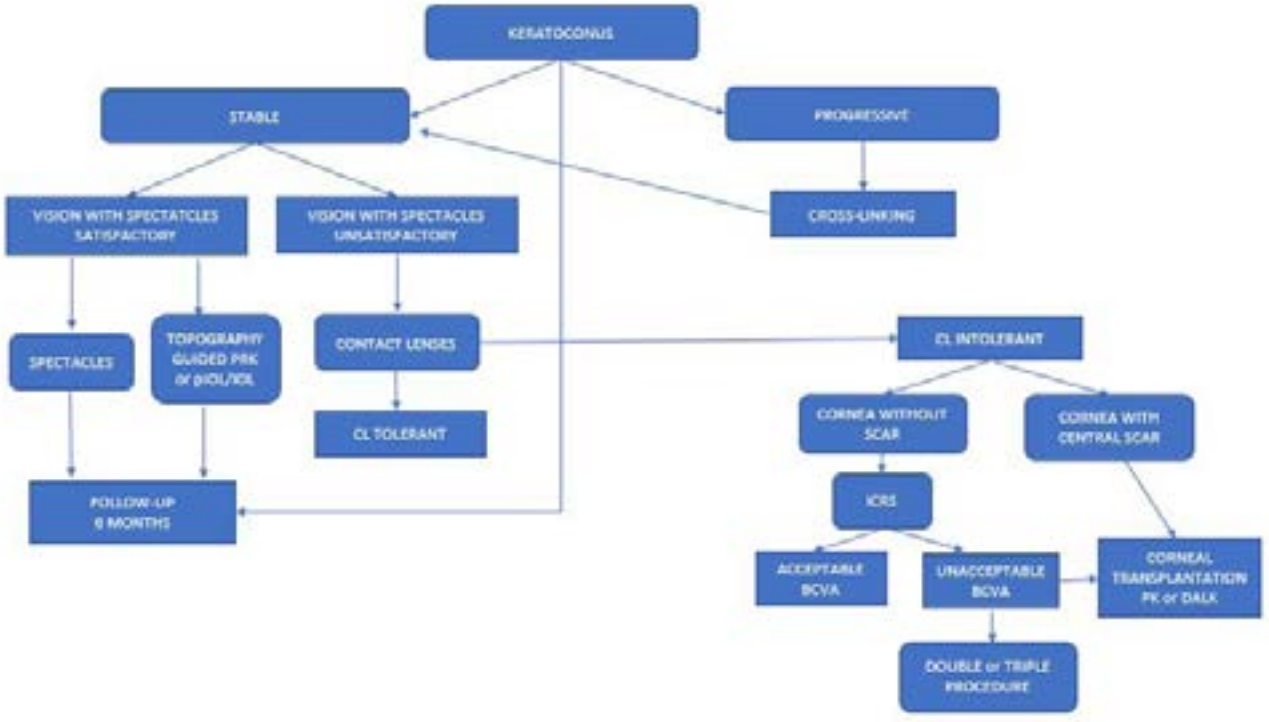
KC is the most common ectatic corneal disease, usually bilateral but asymmetrical. KC, often causes decreased vision, visual impairment, and causing sensitivity to light and glare, is characterized by irregular astigmatism, progressive corneal steepening, protrusion, and stromal thinning.[14]

Histopathologically, primarily corneal epithelium, anterior limiting lamina (Bowman's layer), and stroma are affected compared to the posterior limiting lamina (Descement's layer) and endothelium. As the severity of the disease increases, epithelial cell structure deteriorates, and BL is compromised due to cell loss or damage.[15] Breaks in the Bowman's layer are one of the most common histopathological manifestations, occurring in over 70% of KC eyes.[16] Breaks and deformities in the Descement's layer also have been reported to occur in approximately 20% of KC eyes-typically affecting more severe cases.[17] In particular, surgical treatment options and steps are designed considering these corneal histopathological differences in patients with the disease.

Best treatment options are planned according to the age, stage, progression, risk factors, best corrected visual acuity, corneal topography sign, and compliance of KC patients.[15] Patients are first treated with non-surgical treatment options and then the necessary surgical procedure. Non-surgical treatments are often glasses and contact lenses (soft, rigid gas-permeable, hybrid, and scleral contact lenses). The surgical methods include cross-linking (CXL), intrastromal corneal ring segments (ICRS), and keratoplasty.[18] Several parameters such as corneal thickness, corneal steepness, crystalline lens opacities, patient age, and corneal scarring need to be considered before the selection of the optimal surgical procedure.[19] The keratoplasty techniques, that include PK and DALK, are used as the end-stage KC treatment method.[19] The treatment steps are summarized in Figure 5.

In advanced KC, PK or DALK have been the main options to improve corneal stability and visual acuity. DALK has the unique advantage of involvement of the host endothelium, unlike PK, in which the structural and immunological integrity of the eye is violated. However, both approaches are not exempt from serious intraoperative and postoperative complications, such as suture-related events, corneal or intraocular infections, recurrent epithelial erosions, corneal immune rejection, or late progression of KC in the donor, which could affect donor tissue stability.[20] Hence, there have been ongoing efforts to find a simple surgical alternative that is devoid of the complications associated with PK and DALK.

BLIT has been developed as a new alternative to reduce and stabilize progressive and advanced KC. It consists of the transplantation of an isolated donor Bowman layer within the mid-stroma of a keratoconic cornea.[3,5] This new treatment aims to flatten the recipient cornea, halt the progression of the ectasia, and allow a better tolerance to contact lens wear, and therefore delay or avoid PK or DALK.[3,4] However, it remains to be seen whether it is equal to, or better than current modalities of KC management. If proven successful in the future, it would be another addition in the armamentarium of corneal transplantation surgeons that may be safer than PK or DALK. A BLIT in a keratoconic eye aims to reinforce thin and structurally fragile cornea making it stiffer and flatter. The primary claimed advantage of the procedure is that it may arrest the progression of KC, thereby preserving, and in some cases restoring, contact lens tolerance.[21] As a result, patients may achieve stability of vision and may postpone or avoid surgical alternatives of DALK/PK. The ideal candidates for this technique are those with progressive advanced KC, with good contact lens corrected vision, who are not eligible for collagen crosslinking and have increasingly worsening contact lens tolerance. Patients with associated central scarring are potentially not suitable candidates for the procedure.[21]



BCVA, best-corrected visual acuity; CL, contact lens; DALK, deep anterior lamellar keratoplasty; ICRS, intracorneal ring segments; IOL, intraocular lens; PIOL, pseudophakic intraocular lens; PK, penetrating keratoplasty; PRK, photorefractive keratectomy.

Fig. 5. Flowchart for keratoconus management.

BLIT may have some potential advantages over the more invasive treatment options such as PK or DALK.[3,4,22] First, the ocular integrity is largely preserved with both BLIT options. Second, because the BL is an acellular corneal structure, the risk for allograft rejection may be negligible and consequently medications can be tapered quickly. Third, given that no sutures are used during BLIT, suture-related problems are eliminated and suture removal is not required. Furthermore, donor tissue may be used more efficiently because the donor BL can be dissected from corneas not suitable for PK or endothelial keratoplasty or from the anterior lamellae "leftovers" from previous dissection of an endothelial transplant.[3,4,22]

Clinical results of BLIT in KC

Van Dijk et al. detected that measured simulated and maximum keratometry (Kmean and Kmax) values, mean LogMAR best-corrected spectacle and contact lens visual acuities (BSCVA and BCLVA), and endothelial cell density were stable up to 5 years after BLIT surgery. During all post-operative follow-ups, mean densitometry values were observed higher than preoperatively.[23] At the same time, this study showed an estimated success rate of 84% at 5 years postoperatively.

Zygoura et al., who followed up 7 years the KC patients after BLIT surgery, reported significant anterior corneal curvature flattening of approximately 8D on average within the 1st post-operative month after bowman layer transplantation, especially in more advanced KC cases with more central cones.[24] As a result, this flattening which stabilized up to 5–7 years post-operative is important in terms of preserving or restoring comfortable contact lens wear.

Van der Star et al. reported that the mean logMAR BCLVA for all patients after BLIT did not change from pre-operative up to the last available follow-up, whereas BSCVA improved for patients with pre-operative Kmax >69 D.[25] They detected an estimated success rate of 85% at the 5–8 years follow-up in patients with pre-operative Kmax >69 D, and 75% at the 5–7 years follow-up for patients with pre-operative Kmax <69 D. This study showed that BLIT stabilized KC in particular progressive advanced eyes along with preservation of contact lens tolerance up to 8-year postoperatively.[25]

Luceri et al. evaluated corneal densitometry and higher order aberrations (HOAs) after Bowman layer transplantation and found that HOAs such as spherical aberration decreased for both anterior and posterior corneal surfaces, whereas corneal backscattering increased. However, these

changes did not correlate with best-corrected distance visual acuity.[26]

Post-operative complications were observed in 9% of patients.[7] The complication reported to date is three other eyes of two patients, with a history of severe eye rubbing and atopy, showed acute corneal hydrops at 4.5, 6, and 6.5 years after surgery respectively, despite no evidence of ongoing steepening or thinning.[23,24,27] About 2% of eyes presented with mild contact lens-related keratitis, one at 9 months and one at 75 months postoperatively.[25] One percent of eyes presented with a contact lens-related pseudomonas corneal ulcer at 54 months postoperatively.[25] About 8% of eyes showed post-operative KC progression. [7] About 1% of eyes needed Bowman layer re-transplantation due to an unsatisfactory visual acuity result at 22 months postoperatively.[25] No allograft rejection episodes have been reported up until now.[27]

Challenges of BLIT in KC

The technique of BLIT is a relatively tedious and complex surgical procedure requiring expertise and appears to carry a steep learning curve. Graft rupture may occur during graft preparation, so separating the one-piece Bowman layer requires technique, experience, and attention. Although graft preparation and surgical technique can be challenging, the adaptation of technologies, such as femtosecond laser and intraoperative AS-OCT, may help overcome these barriers to enable Bowman layer transplantation to become a more widely adopted procedure.

Intraoperative complications were observed in 3% of patients. Intraoperatively, the encountered complication is corneal perforation during the mid-stromal pocket dissection, described to occur in 10% (two out of a first series of 22 eyes) of the originally Bowman layer transplantation cohort.[4] Intraoperative perforation of the Descemet membrane occurred in 3% of eyes, with a subsequent PK reported in 1% of eyes.[7,23,28]

BLOT is a more recent surgical procedure described in KC treatment, only preliminary outcomes of a small group of five patients are available.[29] In these preliminary cases, BLOT could be performed successfully, that is the Bowman layer graft could be positioned, flattened, and stretched without wrinkles.

Clinical results of BLOT in KC

Preliminary use of BLOT for the treatment of KC has been explored by Dapena et al.[29] They detected that immediately after surgery, a flattening of the corneal curvature could be observed.[29] Furthermore, a decrease of −5.6 D on average was observed in the Kmax at the 3–6 month follow-ups. No changes were observed in the posterior corneal parameters. After surgery, patients generally showed a high subjective satisfaction level. BSCVA seemed to improve at least 2 lines (or more) in at least half of the cases, and BCLVA remained stable throughout the follow-up period.

On post-operative day 1, all Bowman layer grafts were in position, except for one case, in which the graft showed partial dislocation due to inadvertent removal of the bandage lens.[13] No further dislocations or complications were observed throughout the follow-up period.[29]

Challenges of BLOT in KC

The learning curve in the BLOT technique is easier than in BLIT. Although the graft preparation difficulties were similar, no complications were observed during the grafting of the Bowman layer on the cornea.[27]

2. Post-excimer Laser Corneal Haze

It is known that corneal haze after excimer laser surface ablation causes the best-corrected vision loss and decreased vision quality. Corneal stromal haze seen after excimer laser surface ablation has been shown to be associated with increased ablation depth and aggressive healing response. [30] Besides ablation depth, severity of corneal haze is correlated with excessive ocular ultraviolet radiation, post-ablation epithelial defect duration, male gender, and certain populations with brown iris.[31] Occurrence of corneal haze after photorefractive keratectomy (PRK) been blamed on cytokines and growth factors released in anterior stroma due the destruction of basement membrane, leading to activation of keratocytes which synthesize large-diameter collagen fibrils.[31] Corneal transparency is reduced due to the abnormally deposited extracellular matrix.[31] At present, the options to mitigate the risk of occurrence of haze are either use of intraoperative Mitomycin drops or prolonged post-operative steroids.[32] Both these therapies may have associated side effects and may not be successful in all cases.

BLOT is the new technique that claims to manage corneal scarring and haze seen after PRK. The technique involves superficial dissection of scar followed by isolated BL transplantation. Promising results were seen over 6 months, with no recurrent scarring and improvement in visual acuity with a scleral-supported hard contact lens.[21,22] As mentioned earlier, the postulated cause of subepithelial haze in such cases is a loss of barrier between epithelium and stroma which in turn leads to abnormal wound-healing response. A donor Bowman graft may rebuild the corneal structure

by restoring BL transplantation a normal anatomical barrier between the epithelium and underlying stroma.

Clinical results of BLOT in post-excimer laser corneal haze

Lie et al. reported that the result of BLOT in post-PRK haze has been claimed to be encouraging in early follow-up (6 months), with the case achieving a contact lens-corrected visual acuity of 20/18 from 20/40 within 2 months.[22]

3. Corneal Instability

The first described BLOT case is in which BL onlay grafting was used to reduce fluctuations in visual acuity after previous radial keratotomy (RK). This case reported that BL onlay grafting may have the potential to manage patients with subjective complaints of visual fluctuation in eyes with corneal instability secondary to RK.[33]

Clinical results of BLOT in corneal instability

In their study, Parker et al. reported related to patient with complaints of long-standing diurnal fluctuation in BSCVA after previous RK surgery that BSCVA did not change post-BLOT, but subjective complaints of visual fluctuation decreased. They showed that 5.9 D central corneal steepening, and a completely epithelialized and well-integrated graft, with some minor epithelial remnants located in the pre-existing keratotomy incisions.[33]

4. Corneal Scar

Patients with anterior stromal scarring from prior herpetic keratitis underwent isolated BLOT and showed rapid and complete integration of the BL graft, a significant reduction in anterior stromal scarring, and improvement in visual acuity.[34]

Clinical results of BLOT in corneal scar

In the study of Dapena et al., in which two patients with corneal scarring after varicella zoster virus and herpes simplex virus were evaluated post-BLOT, a significant increase in BCLVA and improvement in corneal clarity was observed. No post-operative complications and reactivation were shown. It has been emphasized that a BL onlay graft may have the potential to reduce superficial corneal scarring and/or anterior corneal irregularities without resorting to deeper keratoplasty in these complex cases.[34]

5. Recurrent Corneal Erosion (Map-dot-fingerprint Dystrophy)

In a case, the transplantation of an isolated BL graft as an onlay proved to be an effective treatment for painful chronic recurrent erosions in the context of map-dot-fingerprint dystrophy in a patient who had undergone numerous other previous treatments without much success.[35]

Clinical results of BLOT in recurrent corneal erosion

Mulders-Al-Saady et al. evaluated the post-BLOT examination of a patient with bilateral map-dot-fingerprint dystrophy and recurrent painful corneal erosions. They reported that the epithelium was smooth on the graft in the postoperative at 1 month and that the patients had no complaints and recurrence of epithelial corneal erosion up to 1.5-year postoperatively.[35]

What is on the horizon?

Recent developments in tissue engineering could make it possible to synthesize and develop a collagenous membrane in situ, which could be transplanted as in BLIT technique. This could possibly lead to a donor tissue-free treatment for the corneal ectasias and other aforementioned stromal disorders that are easily accessible for all patients with no need to eye-banking facilities.

Conclusion

The transplantation of the Bowman layer is an innovative procedure that has been assessed and effectively employed to arrest the advancement of KC in individuals with corneas that are excessively steep or thin for CXL or ICRS treatments. This technique offers the potential for these patients to postpone or circumvent the need for more invasive corneal transplants, such as PK or DALK. While the preparation of grafts and the execution of surgical techniques can present difficulties, the utilization of advanced technologies, such as femtosecond laser and intraoperative AS-OCT, holds promise in addressing these challenges. These technological advancements have the potential to facilitate the widespread adoption of Bowman layer transplantation as a viable procedure.[27]

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