

Preferred practice patterns for photorefractive keratectomy surgery

Rajesh Fogla, Gaurav Luthra¹, Aishwarya Chhabra², Krati Gupta³, Ritika Dalal⁴, Pooja Khamar²

Over the past two decades, excimer laser-based refractive surgery procedures have been successfully established for their safety and satisfactory visual outcomes. Surface ablation procedures or photorefractive keratectomy (PRK) are practised commonly for the correction of refractive errors including myopia, astigmatism and hyperopia. Satisfactory visual outcomes are achieved in majority of cases, although a very small percentage have issues related to corneal haze, regression, and its associated visual disturbances. To ensure optimal outcomes and to minimize complications, certain keys to success have been designed on the basis of the current review of literature on surface ablation procedures.

Key words: Keys to success, preferred practice patterns, PRK

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Ever since its introduction in the early 1990s, Photorefractive Keratectomy (PRK) has been commonly practiced for correction of refractive errors including low to moderate myopia, astigmatism, and hyperopia.^[1-3] PRK procedure involves epithelial removal and subsequent laser ablation of Bowman's layer and the anterior stroma. Despite good visual outcomes, a shift to flap-based procedure i.e., Laser in-Situ Keratomileusis (LASIK) was noted in the early 2000s to obviate postoperative pain and risk of corneal haze associated with PRK.^[4,5] Epithelial defect in PRK results in direct exposure of nerve endings causing undesirable pain, usually short-lived, and can be addressed effectively by using various measures.^[6] Corneal haze post-surgery is an unwanted adverse outcome of PRK with an incidence of 1.4%, which can often lead to loss of best-corrected visual acuity.^[7] Studies have shown the effectiveness of using intraoperative topical 0.02% Mitomycin-C (MMC) application on stromal bed following PRK to limit occurrence of corneal haze.^[8]

Despite these drawbacks, PRK is a procedure of choice in the following subjects^[9,10]:

- Central corneal thickness less than 500 microns but not less than 475 microns.
- Flat corneas (<41 D)
- Steep corneas (>48 D)
- Epithelial basement membrane disease,

- Anterior basement membrane dystrophy,
- Recurrent corneal erosions,
- Predisposition to contact injury,
- Narrow fissures
- Thin corneas where the stromal residual bed may be less than 250 to 300 microns
- Deep orbits leading to inadequate exposure for microkeratome blade who are ineligible for LASIK.

This article gives an insight into visual outcomes post PRK, role of PRK Xtra procedure in current day refractive practice, and applications of PRK in management of irregular cornea. It will also guide the clinicians on factors influencing haze formation which is one of the most common complication post PRK, and provide measures to manage the same following an algorithmic preoperative, intraoperative and postoperative approach to ensure optimal visual outcomes.

Visual Outcomes of PRK in Comparison to Small Incision Lenticule Extraction (SMILE) and LASIK

Gershoni *et al.* reported Trans-PRK and femtosecond LASIK (FS LASIK) both have excellent efficacy, safety, and predictability.^[11] Sia RK *et al.* in their study found, patients undergoing SMILE, LASIK, and PRK had excellent and comparable outcomes in terms of safety, efficacy, predictability, and stability.^[12] On comparing SMILE vs PRK, they found SMILE was had slightly

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Senior Consultant, Cataract, Cornea and Laser Refractive Surgeon, Director Cornea Clinic, Apollo Hospitals, Hyderabad, Telangana, ¹Cataract and Refractive Surgeon, Director, Drishti Eye Institute, Dehradun, Uttarakhand, ²Department of Cataract and Refractive Surgery, ³Cornea and Refractive Surgery, Narayana Nethralaya, Bangalore, Karnataka, ⁴Refractive Surgeon and Dry Eye Specialist, Dr Dalal's Clinic, Mumbai, Maharashtra, India

Correspondence to: Dr. Pooja Khamar, Consultant, Cataract and Refractive Surgery, Narayana Nethralaya, 121/c, West of Chord Road, Rajajinagar, Bengaluru, Karnataka, India. E-mail: dr.poojakhamar@gmail.com

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better visual outcomes at the end of 1 month postoperatively with respect to UDVA. However, at 3 months postoperatively, PRK group outperformed SMILE with respect to percentage of eyes achieving UDVA of 20/20 or better (99.6% vs 95.1%, respectively).^[12]

El-Agha MS *et al.* in their study compared the efficacy and safety of PRK and LASIK in the treatment of spherical hyperopia and concluded that the two procedures were of comparable in their efficacy and safety.^[13] Wang Y *et al.*, concluded that SMILE is a feasible and effective procedure for treatment of hyperopia however, long-term studies are required to improve the predictability and visual outcomes of the procedure for hyperopic refractive correction. Also, SMILE is not deemed suitable for management of simple or compound hyperopic astigmatism.^[14] Further, studies comparing the visual outcomes post hyperopic SMILE and PRK are required.

Biomechanical Strength of the Cornea Post PRK

Francis M *et al.* in their study concluded eyes that underwent PRK had the least decrease in their stiffness parameters as measured on Corvis-ST (OCULUS Optikgerate GmbH, Wetzlar, Germany) before and after the procedure in comparison to LASIK and SMILE that caused a much greater decrease in stiffness parameters.^[15]

PRK Xtra

PRK Xtra is a procedure wherein a simultaneous crosslinking (KXL) is performed in addition to PRK. Studies reported on PRK Xtra have been performed only for myopic correction.

PRK Xtra is the procedure of choice in the following cases:^[16]

- Corneal pachymetry between 450 and 474 μm with normal corneal topography.
- Or cases with subtle tomographic abnormalities but not suggestive forme fruste or subclinical keratoconus - mild inferior-superior asymmetry or the overall D on the Belin / Ambrósio Enhanced Ectasia Display (BAD-D) map in red zone.

Total UV-A energy exposure in combined refractive surgery and concurrent KXL varies from 2.7J/cm² to 5.4J/cm².^[16-18] The indication for performing KXL with refractive procedure is prophylactic rather than therapeutic and is performed in normal eyes. Hence a lower UV-A total energy can be used. The number and severity of complications are lower with a lower total energy. KXL with accelerated protocol results in reduced keratometric flattening as compared to conventional KXL.^[19]

PRK Xtra has shown similar or better refractive outcomes and stability as compared to PRK only.^[16,18] Lee *et al.* performed a 1-year comparative study which showed that the postoperative uncorrected visual acuity (UCVA) at 1 year did not show any statistically significant difference ($P = 0.289$) between the two groups.^[17] Sachdev *et al.*, in their 1-year comparative study reported no significantly different in both groups although the patients who underwent PRK Xtra had a statistically significant thin corneas ($P < 0.01$) with corneal topographic abnormalities ($P = 0.02$).^[16]

Studies have reported that PRK Xtra is safe for myopia correction.^[16,18] Post-operative endothelial cell counts were similar between the two groups.^[16,18] Lee *et al.* reported a case of sterile marginal infiltrate in the early postoperative period in a

patient who underwent PRK Xtra which resolved after topical steroid application.^[18] The final visual outcome remained unaffected in this case.^[17] Sachdev *et al.* reported 9 eyes in PRK Xtra group developed grade 1 superficial corneal haze which subsequently resolved in 6 months post-surgery.^[16]

Role of PRK for Retreatment in Cases of Suboptimal Laser Vision Correction and Irregular Cornea

Successful corrections with the use of PRK have been reported in cases of cornea scar as a result of full-thickness penetrating corneal trauma and elliptical ablation post Epi-LASIK.^[20]

PRK Post LASIK

Residual overcorrection, under-correction, and induced astigmatism following LASIK may require retreatment. Flap relief or flap recutting is the most commonly used technique for retreatment post LASIK. Buttonholing, relatively low residual stromal bed, and difficulty on identifying the flap edge are the limitations of this surgical option.^[21-23] Increased risk of epithelial ingrowth, flap tear, striae, and diffuse lamellar keratitis have been reported with re-lifting of the old flap.^[21] The flap associated complications can be avoided by the use of photorefractive keratectomy for re-corrections.

PRK Post Penetrating Keratoplasty

Penetrating keratoplasty patients suffer from postoperative refractive error. Partial resolution of these refractive errors can be done using LASIK and PRK. LASIK has many advantages like earlier visual rehabilitation, lesser chances of irregular astigmatism, and post-surgical regression, but it is associated with graft rejection, dry eye, and high-order aberrations.^[24] PRK on the other hand is a safer option but it is associated with corneal haze and postoperative regression over time. However, these PRK associated complications can be minimized using new medications.

PRK Post Radial Keratotomy

Radial keratotomy was commonly used for the treatment of myopia in the past. Prospective Evaluation of Radial Keratotomy (PERK) study reported that about 43% post-RK patients develop hyperopia.^[25] LASIK has successfully been used for the treatment of post-RK induced hyperopia and residual myopia, but it is associated with complications like extension of RK incisions.^[26] PRK appears to be a better option in these patients as it avoids these complications.

Corneal Haze Post PRK

Post-PRK haze can be classified on the basis of severity and time of onset as 'Early' and 'Late' haze. Stojanovic and Lipshitz *et al.* defined "Early haze" as more common and transitory in nature. It is noted between 1 to 3 months after PRK due to gradual development of subepithelial collagen and extracellular matrix at the epithelial-stromal junction.^[27,28] It is rarely associated with clinical symptoms and tends to disappear within 1 year of surgery. Whereas, "Late haze" tends to appear anytime from 2 months to even years after surgery and is typically reticular in pattern. It is characterized by epithelial injury and depends on cornea stromal remodeling. Late-onset haze is more unpredictable and has a higher probability of impairing vision.^[27]

Corneal haze post PRK must be differentiated from the haze post corneal collagen cross-linking. Clinically, the PRK-related corneal haze is subepithelial in nature with a reticulated appearance. On the other hand, the corneal haze after cross-linking is transitory and disappears after a few months. It is seen in the stroma anterior to the demarcation line and had a dust-like appearance most likely resulting from lacunar oedema of the keratocytes.^[29]

Mechanism of Haze

The safety and efficacy of any refractive procedure depends on the corneal wound healing. The corneal wound healing is a complex cascade which is initiated immediately after injury to the epithelium. There is release of multiple growth factors and cytokines like TNF- α , MMP-9, interleukin (IL)-1 α and IL-1 β , platelet-derived growth factor which cannot penetrate the intact epithelial basement membrane to reach stroma.^[8] The integrity of epithelial basement membrane (EBM) plays a significant role in the pathophysiology of corneal haze.^[30]

Under optimal wound healing conditions, corneal injury or surgery initiates a pro-inflammatory phase characterized by release of inflammatory mediators like MMP-9, IL-6,

TNF- α etc., into the stroma. This leads to the activation of keratocytes and their differentiation into myofibroblasts. The myofibroblasts promote collagen remodeling. This is followed by the release of fibronectin which causes apoptosis of myofibroblasts.^[31,32] The end result is a clear cornea with the restoration of its normal structure and function [Fig. 1].

Any hindrance such as inflammatory conditions, irregular stromal surface or death of large number of keratocytes as seen after surface ablation for high myopia can lead to defective EBM regeneration.^[31,32] There is also altered wound healing response primarily due to TGF- β signaling pathway causing an excessive formation of myofibroblasts and fibroblasts.^[31] These myofibroblasts with contractile properties and less transparency lead to deposition of disorganized cellular material with abnormal extracellular matrix remodeling of the stroma. These events in turn lead to scattering of light and corneal haze.^[31,33,34] [Fig. 2].

Additional factors like nutritional deficiency, change of geographic location or inflammation during the healing phase may lead to the development of late-onset haze.^[11] Other risk factors associated with corneal haze include exposure to UV-B rays, atopy, small ablation zone, autoimmune diseases, keloid and age.^[28,35-37]

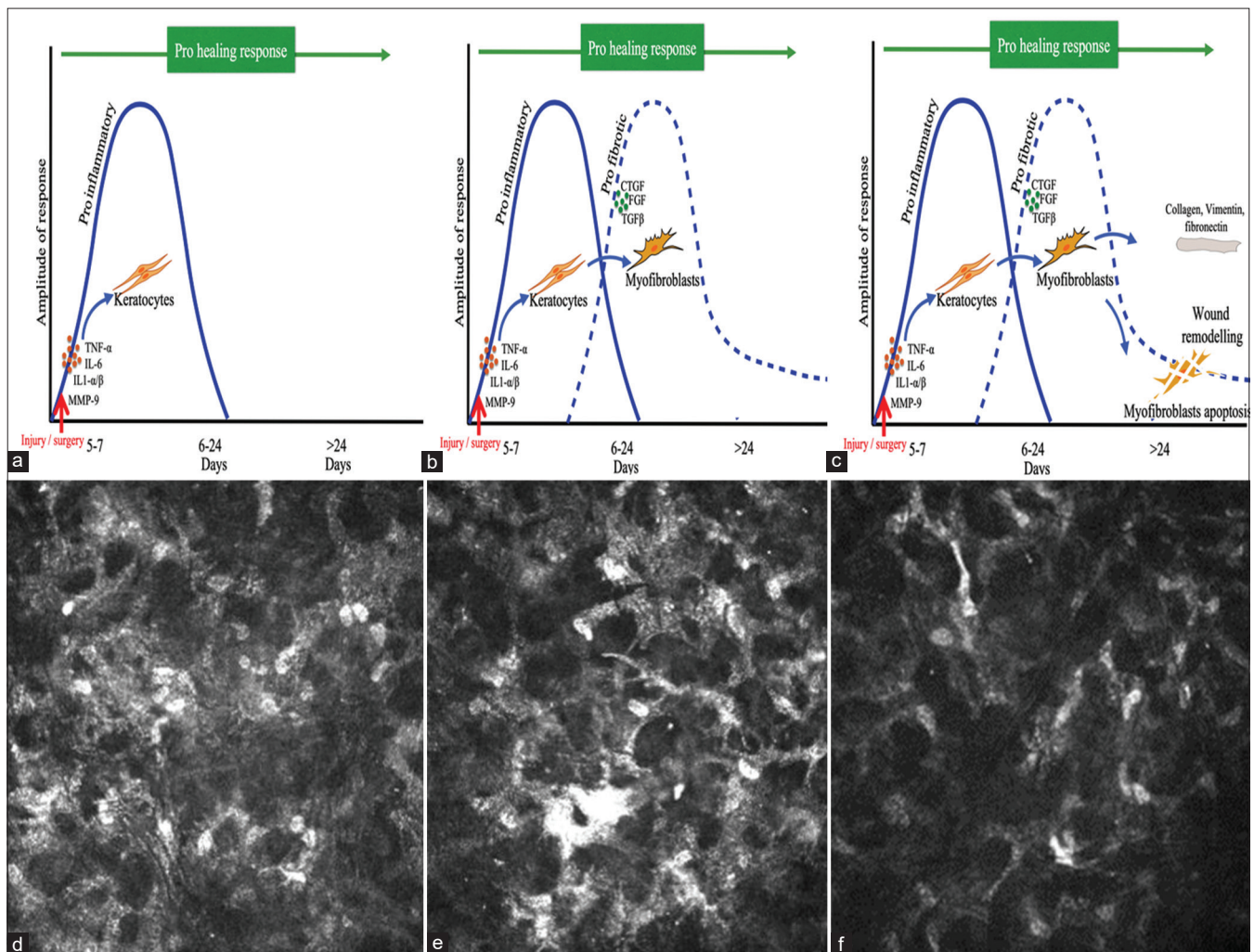


Figure 1: Normal corneal wound healing post injury/surgery. Graph showing phase of activated keratocytes (a); corresponding *in vivo* confocal microscopy (IVCM) picture (d) Graph showing phase of myofibroblast and fibroblast (b); corresponding IVCM picture (e) Graph showing phase of apoptosis (c); corresponding IVCM picture (f)

Novel Inflammatory Markers in Predicting Post PRK Haze

The corneal wound healing response is predominantly contributed by the corneal epithelial cells which secretes growth factors like TGF- β and cytokines. These factors promote migration of stromal keratocytes and their differentiation into myofibroblasts.^[8] It was hypothesized that any pre-existing alteration in the molecular profile might lead to the activation of alternate pathways stimulating post-surgery haze. For better understanding of these molecular mechanisms, Kumar *et al.* performed a detailed analysis of 'haze predisposed' individuals who developed haze which persisted for more than 6 months after PRK surgery. Micro-array analysis of the epithelium collected from these patients at the time of surgery revealed dysregulation of genes linked to various pathways like WNT pathway, extracellular matrix related pathways, etc.^[37]

Role of Mitomycin-C (MMC) in Preventing Corneal Haze Formation

MMC is an antimetabolite which inhibits fibroblast proliferation and differentiation, thereby blocking myofibroblast formation responsible for subepithelial haze.^[38] Since the first description

of use of 0.02% MMC in PRK to minimize risk of haze, it has now become a routine procedure among refractive surgeons performing surface ablations.^[39] Possible side effects of MMC use are corneal melt, raised variability in refractive outcomes, and endothelial cell loss.^[40,41] Coelho *et al.* studied the effects of varying concentration of MMC (0.02% and 0.002%) on cornea and found similar effects on haze.^[42] In cases of high myopia, MMC application is effective in preventing postoperative haze at 1 to 3 months but not at 6 to 12 months after surgery.^[43] Thus, along with the use of MMC, alteration of predisposing factors leading to inflammation can help further reduce the incidence of haze.

The fundamental goal of refractive surgery is to optimize predictability. To enhance the predictability of the visual outcomes, we have developed an algorithmic approach for the detailed assessment of the patients, triaging them according to the severity of symptoms and managing them to attain an optimal PRK surgery outcome.

Preoperative Evaluation

History

- Ocular/systemic illness:** Detailed evaluation of clinical history is recommended to look for signs of ocular

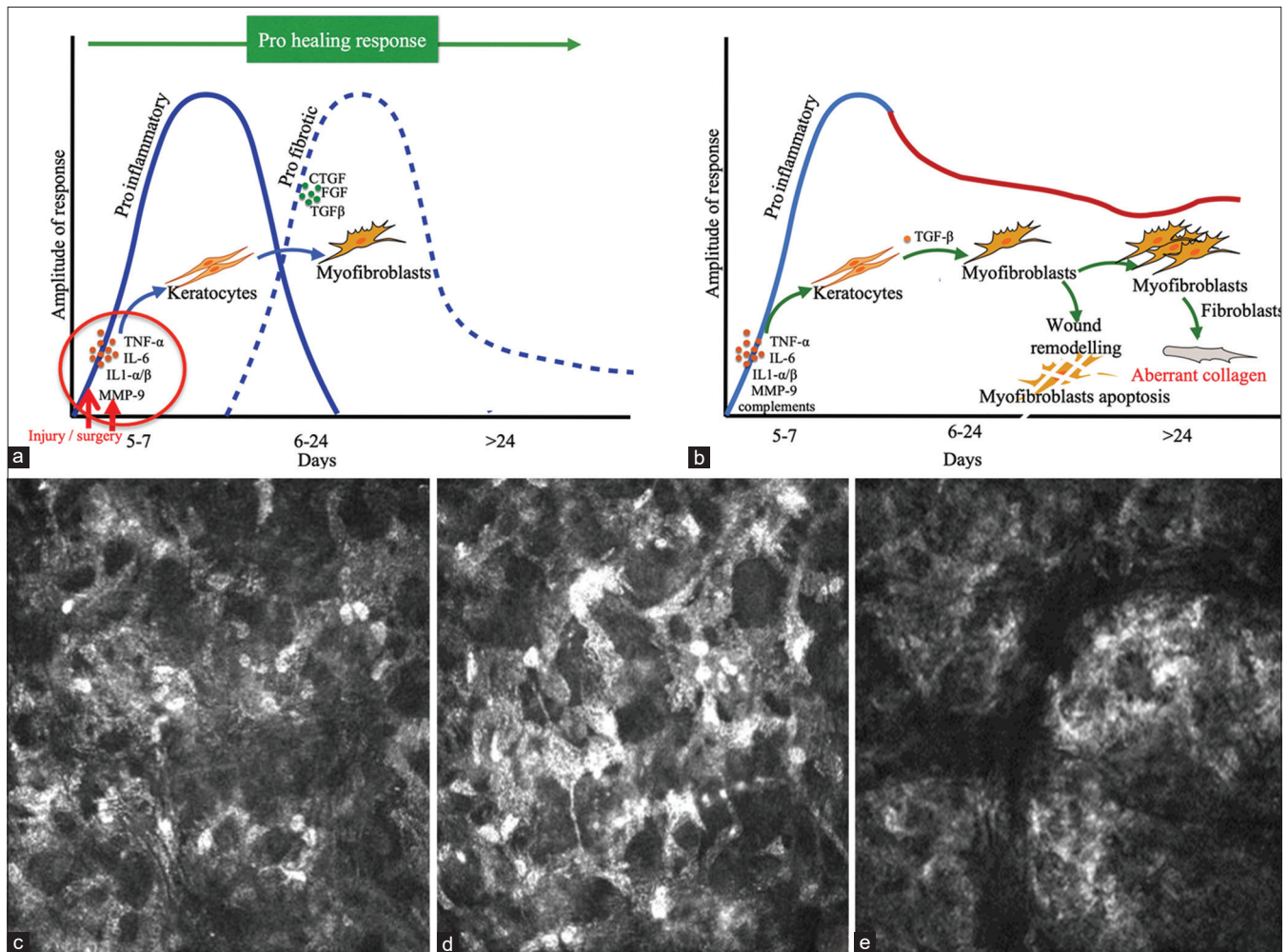


Figure 2: Corneal wound healing post injury/surgery under abnormal conditions. Graph showing phase of excessive activated keratocytes (a); corresponding IVCM picture (c) Graph showing phase of excess myofibroblast, fibroblast and aberrant collagen formation (b); corresponding IVCM picture of the phase of excess myofibroblast and fibroblast (d); aberrant collagen formation (e)

allergy-like eye rubbing, itching, burning sensation, etc., and history of any systemic symptoms like acne, keloid, etc.

2. **Contact lens intolerance:** Chronic contact lens usage may lead to dryness and evokes a cascade of pro-inflammatory responses on the ocular surface which manifests as ocular pain, discomfort, and intolerance to contact lenses.^[44] The presence of intolerance to contact lenses is thus, depictive of unhealthy nerves and an unhealthy ocular surface suggestive of inflammation.^[45]
3. **Working environment:** Another factor which is known to play a significant role is the working environment of the individual. Studies have proven that there might be an increased risk of late-onset haze in patients with moderate to high myopia who are exposed to high UV radiation level.^[28]

Examination

1. **Tear break-up time (TBUT):** TBUT helps in the assessment of tear film stability. In cases of Meibomian gland dysfunction, there is an inadequate secretion of lipid layer which causes instability of tear film. The tear film instability leads to initiation of an inflammatory cascade.^[46] A value of more than 10 seconds is considered as normal.^[47]
2. **Meibomian Gland Dysfunction (MGD):** It is associated with qualitative and quantitative changes leading to dropout or loss of Meibomian glands. It also involves the release of fatty acids by bacterial lipases inducing cell-mediated inflammation which affects the integrity of epithelium of ocular surface.^[46] Non-invasive infrared meibography can be used for the quantitative assessment of Meibomian gland drop out which correlates to the severity of the disease.^[47,48]
3. **Ocular Surface Disease Index (OSDI):** OSDI questionnaire score has been shown to correlate strongly with the density of dendritic cells in the cornea which is a marker of inflammation.^[48] It is a simple tool to assess the patient's symptoms and captures aspects of ocular surface inflammation with excellent sensitivity and specificity.^[49]

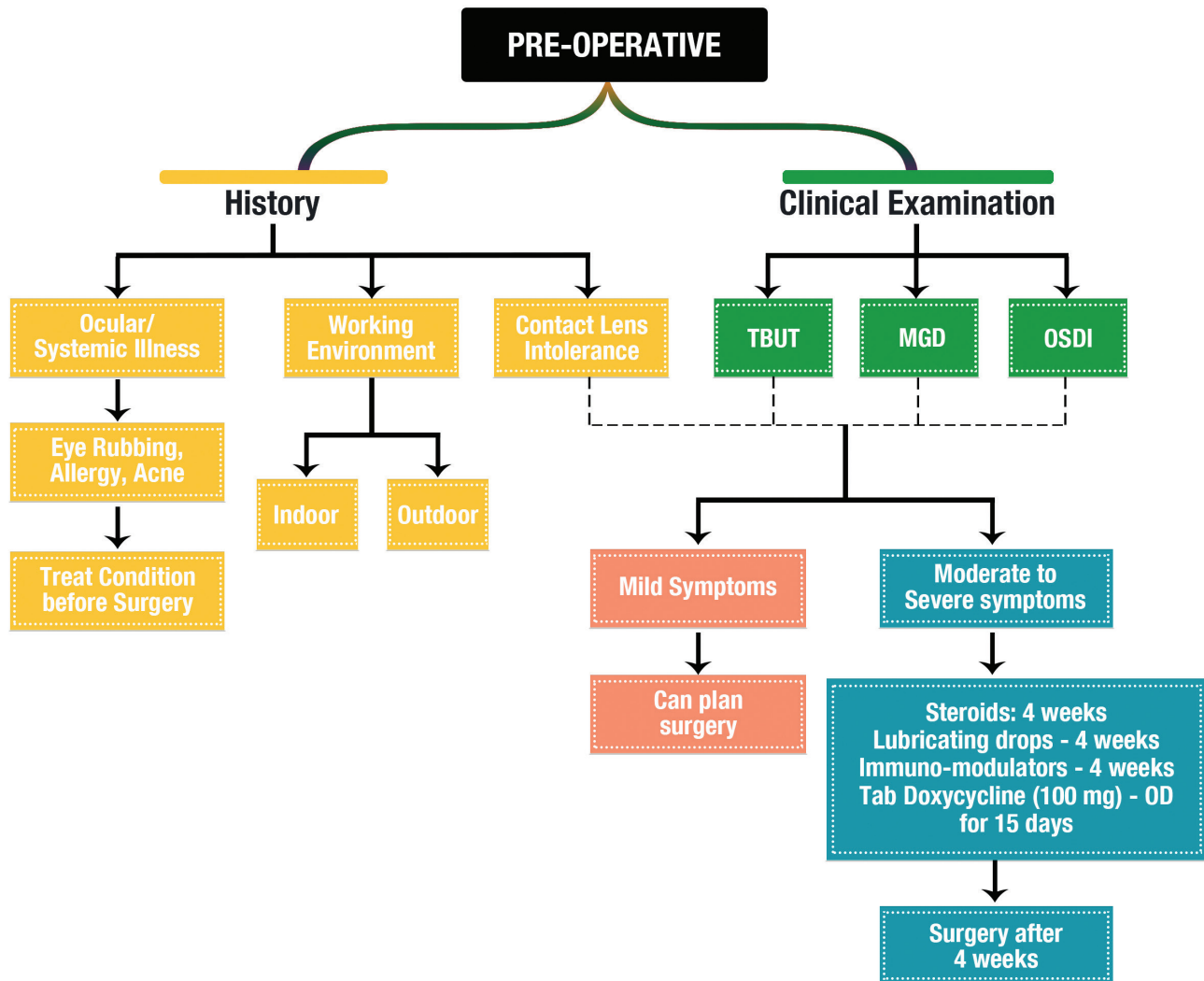
Preoperative Considerations

1. Patients who lack any signs or symptoms are directly taken up for surgery without any intervention.
2. For the patients who show signs of inflammation and an unhealthy ocular surface, a multimodal approach is adopted before taking them up for surgery [Table 1].
 - i. Copious supplementation of preservative-free artificial tears is advised as it flushes away the irritants and prevent inflammation of ocular surface. Use of lubricating eye drops with preservatives can lead to toxicity and delayed healing of ocular surface.^[50,51]
 - ii. A short course of topical anti-inflammatory drugs such as topical steroids in tapering dose and topical immunomodulators is prescribed for 4 weeks to ensure a healthy ocular surface, less pain during the procedure and to minimize post-operative complications.^[51,52] Laccheri *et al.* have proven that topical cyclosporine has a low-risk profile, better tolerance, and offers improved control in chronic inflammation.^[53]
 - iii. Topical drugs are supplemented with a short course of oral doxycycline (100 mg), once a day for 15 days in patients with MGD, blepharitis, and acne.^[54] Therapeutic efficacy of oral Doxycycline has been attributed to its anti-inflammatory effects, promoting tear film stability and ocular flora alteration.^[55]

Intraoperative Considerations

1. **Techniques of epithelium removal** - The first step of PRK surgery is removal of epithelium to reprofile the stroma by exposing it to excimer laser.^[6] Various safe and effective techniques of epithelium removal are available in our armamentarium currently. For a successful visual outcome, a smooth Bowman's layer is essential.^[56]
 - i. **Mechanical debridement** can be done using a blunt spatula or hockey stick knife. Care should be taken to ensure complete epithelial removal without any damage to the Bowman's membrane.^[57]
 - ii. **Alcohol-assisted PRK** using 20% ethanol facilitates complete removal of epithelium with less variability and more comfort for the patient when compared with mechanical debridement.^[58] However, studies have shown that ethanol can have a cytotoxic effect on the corneal epithelial cells and keratocytes and may delay re-epithelialization.^[59]
 - iii. **Trans-epithelial PRK (TransPRK)** is a newer technique which uses the PTK mode to remove the epithelium followed by excimer laser ablation. This **two-step procedure** is not widely used as it is more time consuming, with a potential to cause corneal dehydration, limited accuracy, and causes a hyperopic shift.^[60]
 - iv. **Single-step TransPRK** is the most recent technique of epithelium removal promising results. Reports suggest reduced risk of postoperative pain, dry eye, haze, and a quicker re-epithelialization. Some studies have revealed improved efficacy of single-step TransPRK over alcohol-based and mechanical debridement while others have indicated comparable results.^[61]

Lee *et al.* showed similar safety and efficacy of all epithelial removal techniques (PRK, trans-PRK) for treating a wide range of myopia. There was no significant difference between the procedures in terms of pain and visual outcomes. Mechanical removal of the epithelium may lead to microtrauma to the Bowman's membrane and retention of islands of epithelium whereas trans-PRK leaves behind a smooth stromal bed to facilitate better re-epithelialization.^[60]
2. **Mitomycin-C (MMC)** - MMC is usually recommended in 0.02% concentration for 15 – 90 seconds, for ablations >-2 dioptres or ablation depth ≥ 50 microns, and for retreatments.^[62] Care should be taken to avoid touching the limbus with the Mitomycin-C soaked swab followed by a thorough wash of the ocular surface with cold Balanced Salt Solution (BSS) to avoid side-effects as mentioned above.^[6]
3. **Bandage contact lens (BCL)** - It is used therapeutically to augment healing of the epithelium. The healing effect differs according to the oxygen permeability, thickness, water content of the BCL used. Studies have shown that out of the various contact lenses available for use, senofilcon A provides more comfort than lotrafilcon A because of its high water content. Etafilcon A had a high pain score because of its low oxygen transmissibility. Hydrogel silicon contact lenses with high oxygen permeability reduce peri-operative pain, accelerates re-epithelialization, and reduce the patient discomfort.^[63] Thus, using Hydrogel silicon contact lenses can be beneficial for optimal healing and patient comfort.
4. **Pain management** - Thorough irrigation with cold BSS after excimer laser helps in diminishing its thermal effect and reduces the release of inflammatory mediators which are responsible for inducing pain after the procedure.^[64] We

Table 1: Pre-operative algorithm

recommend the use of soft BCL soaked in preservative-free Ketorolac Tromethamine 0.45% ophthalmic solution which is placed over the cornea after the procedure for 1-3 days till complete re-epithelialization.^[6] [Fig. 3] Studies have also proven that Ketorolac is known to reduce the levels of pro-inflammatory markers like Interleukin-6 (IL-6). It inhibits cyclo-oxygenase enzyme, prostaglandin production and leads to diminution of IL-6 response. Thus, it may also aid in controlling the severity and intensity of postoperative adverse events.^[65] Limited application (for 1-3 days) of BCL with topical Non-steroidal anti-inflammatory drugs (NSAIDs) adsorbed on it after excimer laser ablation thus prevents inflammation and provides long-lasting analgesia with minimal risk of side effects like delayed healing, corneal melting, etc.^[6,66]

Postoperative Considerations

1. Pain management: Along with the use of soft BCL soaked with topical NSAIDs, intraoperatively a multimodal approach is followed to tackle post-PRK pain. Topical NSAIDs, topical opioids, topical cycloplegics, oral analgesics, oral

anti-convulsant, avoiding exposure to sunlight are some of the modalities which are used extensively in an attempt to provide pain relief.^[4,6] Topical NSAIDs effectively reduces pain by preventing the release of prostaglandins which are the major mediators of nociception. Use of pregabalin and gabapentin has been proven to be beneficial by some studies as they inhibit the nerve impulses and help in reducing pain.^[66]

- The use of anti-inflammatory drugs in the form of topical steroids is recommended for 8-12 weeks in tapering dose, the duration of which depends upon the depth of ablation and the preoperative condition of the ocular surface. Along with this, topical immunomodulators and preservative-free lubricants are prescribed for 6 months [Table 2].^[51,52]
- Attention must be paid to the lid margins in terms of prior MGD diagnosed at the time of preoperative evaluation. Unhealthy lid margins must be treated aggressively along with complete course of oral doxycycline.^[53]
- Few studies have shown a prophylactic effect of oral vitamin C supplementation against post-PRK haze formation.^[67] It is thus necessary to maintain optimal serum levels of Vitamin C in all the patients.

- 5. Use of UV protectant glasses is advised after surgery to avoid exposure to harmful UV radiation for 8-12 months.^[68]

Follow-Up and Evaluation

Preoperatively, all the patients who are prescribed any topical or systemic medications are re-evaluated at the end of one week

to ensure a healthy ocular surface before proceeding with the surgery. Postoperatively, the patients are advised to strictly follow the schedule of visits on first day, one week, at the end of one month, three months, and six months after surgery. At every visit, a detailed assessment is carried out which

Table 2: Post-operative Treatment algorithm and treatment of Late onset corneal haze

POST – OPERATIVE

Late Onset Corneal Haze

- ▶ Topical Steroids: 8-12 weeks in tapering dose
- ▶ Preservative free lubricating eye drops: 4 times a day for 6 months
- ▶ Tacrolimus eye ointment: 0.03% - HS for 6 weeks
- ▶ Tab. Doxycycline (100 mg)(MGD, Acne): OD for 15 days
- ▶ Vitamin C (500 mg): TDS for 3 months
- ▶ UV protectant glasses for 8 - 12 months

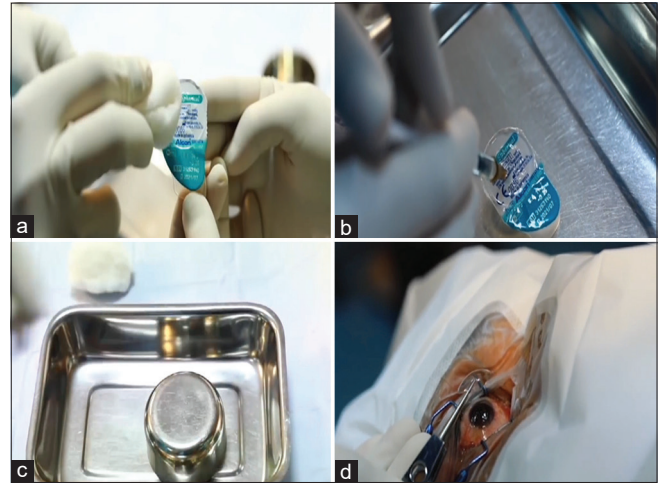
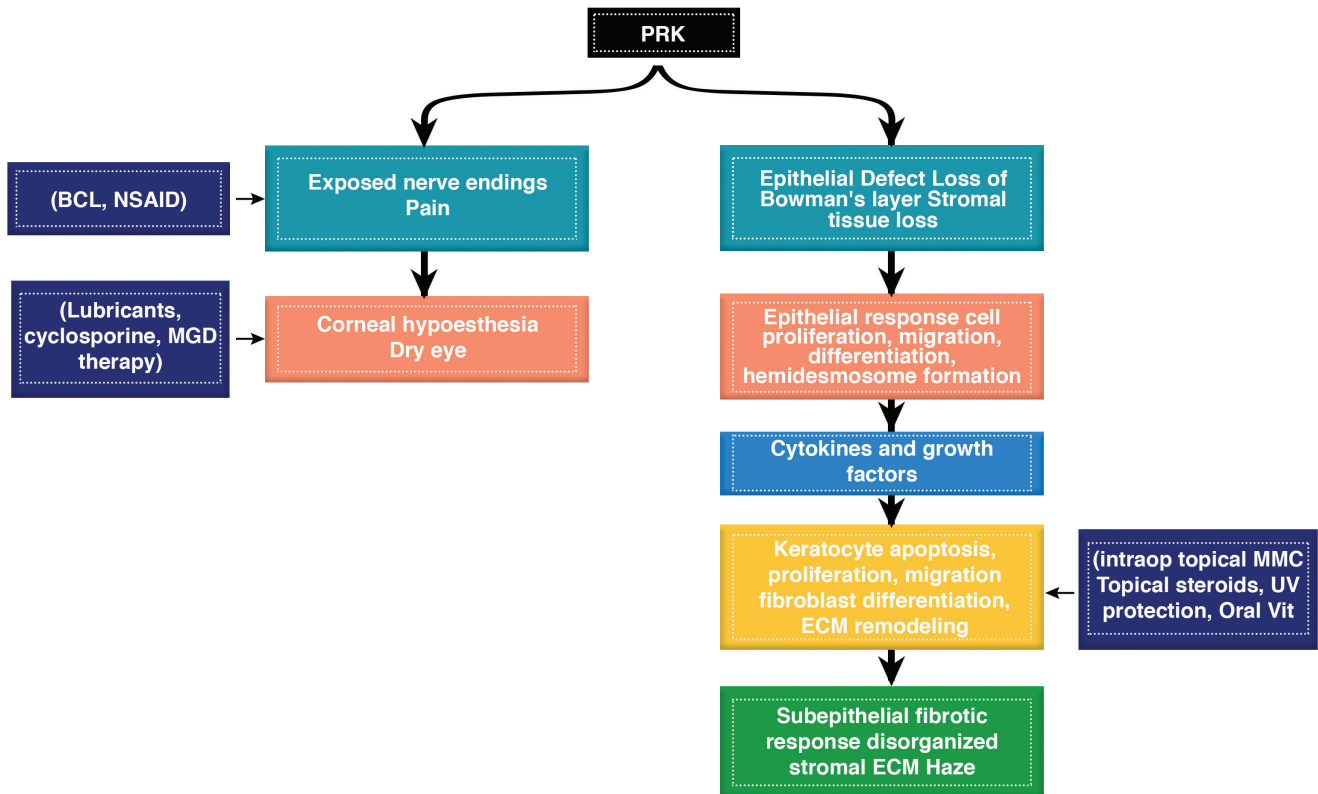


Figure 3: Preparation of preservative-free ketorolac tromethamine 0.45% soaked BCL for pain management. Cleaning the outer surface of the contact lens packet with gauze piece soaked in 99.99% ethyl alcohol (a); injecting 0.2 ml preservative-free Ketorolac Tromethamine 0.45% into the contact lens solution using a tuberculin syringe (b); keeping the Ketorolac soaked contact lens in a sterile container for 20 minutes (c); placing the contact lens on the patient's eye at the end of the procedure (d)

Table 3: Summary for pathophysiology of healing post PRK surgery and stepwise management



includes Intraocular Pressure (IOP) measurement, Slit-lamp biomicroscopy, and corneal topography. Any symptoms or signs if identified, are documented and aggressively treated.

Late-Onset Clinical Haze

Long term treatment is advised to the patients who develop "late-onset clinical haze" post-PRK. Any ocular (MGD, allergy, eye rubbing), local (acne) or systemic inflammatory signs should be looked at carefully and treated accordingly. Topical steroids are prescribed for 8-12 weeks in a weekly tapering dose. Ensure adequate lubrication, optimal serum levels of Vitamin C, and UV protectant glasses for 8-12 months.^[67,68] To control inflammation, steroids are supplemented with topical immunomodulator ointment for 6 weeks and oral doxycycline for 2 weeks^[69] [Table 2].

Conclusion

PRK one of the refractive procedures which gives excellent visual outcomes. Patient selection and counseling are major cues to the success of PRK. PRK can also be used in management of post keratoplasty associated refractive error, irregular astigmatism, and refractive surgery in thin cornea in combination with CXL. Major drawbacks of PRK surgery include postoperative pain and haze. Pain mitigation is carried out by curbing the cascade of events at various levels. To limit haze, a meticulous approach is adopted which includes a comprehensive history, clinical examination, and laboratory investigations [Table 1]. Based on this assessment, a decision is made to treat the symptoms first or to take the patient directly for surgery and their postoperative management [Tables 2 and 3]. Thus, adequate measures taken at the right time are of utmost importance in halting the development and progression of such haze both in short and long term. Accurate identification and management of risk factors preoperatively along with the appropriate measures taken at each step of the surgery may prove to be the invaluable keys for a successful post-PRK outcome.

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Conflicts of interest

There are no conflicts of interest.

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