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Taking a Different Point of View: The Utility of Endoscopic Vitrectomy

Flavio A. Rezende, MD, PhD
Thiago Machado Nogueira, MD

Introduction

Pars plana vitrectomy (PPV), introduced by Dr. Robert Machemer in the 1970s, revolutionized the treatment of vitreoretinal diseases. Technological advancements, such as the development of small-gauge instrumentation and wide-angle viewing systems, have since enhanced the precision and safety of these procedures.[1] However, microscope-based visualization remains limited in scenarios involving limited anterior segment transparency, or when accessing anatomical areassuch as the anterior vitreous base, ciliary body, and retroirideal space.[2]

Endoscopic vitrectomy overcomes these limitations by offering direct intraocular imaging from the probe tip, bypassing anterior segment opacities, and yielding an unobstructed, distortion-free view of otherwise hidden structures[3-6] **(Figure 1)**. This technique allows for dynamic adjustment of perspective and orientation, enabling access to the peripheral retina, anterior vitreous base, and retroirideal structures not easily visualized with traditional top-down microscope-based views[7] **(Figure 2 and Table 1)**. Modern endoscopy systems combine miniaturized probes,[8] high-resolution video capture, coaxial illumination, and enhanced manoeuvrability, making them valuable tools in both routine and complex cases.[4,9]

This review explores the evolving role of endoscopic vitrectomy by examining its principles, instrumentation, clinical applications, surgical techniques, limitations, and future directions—demonstrating how a shift in visual perspective can broaden the capabilities of modern vitreoretinal surgery.

Principles and Instrumentation

Ophthalmic endoscopy was first employed by Thorpe in 1934 using a 6.5 mm probe to remove intraocular foreign bodies (IOFBs). The original device featured external illumination and integrated forceps. By 1978, Norris and Cleasby developed a 1.7 mm intraocular endoscope for use in orbital and intraocular procedures. A pivotal advancement occurred in the 1990s when Uram introduced fiberoptic endoscopes capable of transmitting real-time intraocular images to external monitors, achieving a resolution of up to 17,000 pixels.[10,11] These early instruments laid the groundwork for contemporary videoendoscopic systems that now feature substantial improvements in size, image quality, and functionality.

Contemporary systems use 19- to 25-gauge probes that integrate imaging, illumination, and optional laser photocoagulation capabilities.[2,3,5] Smaller gauges offer improved intraocular fluidics control but compromise resolution. These devices operate via coaxial light and image capture at the probe tip, allowing for a 360° panoramic visualization of the posterior segment independent of corneal clarity, lens status, or pupillary dilation. Unlike microscope-based systems, endoscopy employs coaxial lighting and captures reflected light directly from intraocular tissues, allowing enhanced visualization of otherwise transparent structures such as the vitreous - which appears more opaque in the endoscopic view.[12]

Both straight and curved endoscopy probes are available for intraocular surgery, each offering distinct advantages and limitations. Straight probes are generally favoured for their simplicity in orientation, reduced rotational complexity, and ease of use, particularly for surgeons who are new to endoscopic techniques. Their alignment with traditional instrument handling makes them more intuitive, thereby minimizing disorientation during surgery. However, straight probes may be limited in accessing anatomically challenging regions. In contrast, curved probes are designed to enhance manoeuvrability around intraocular structures, providing improved access and visualization in complex cases where angled views are essential.

Its curved tip, however, introduces an additional axis of rotation, which can complicate spatial orientation and contribute to a steeper learning curve[12] **(Figure 3)**.

The base unit of a typical endoscopic vitrectomy system currently includes a xenon or LED light source, digital image processing modules, a high-definition monitor, and an optional laser source, with the possibility of heads-up displays integration[10] **(Figure 4)**. Optical fibre bundles housed within protective sheaths run from the console to the intraocular probe, each bundle dedicated to a specific function—illumination, imaging, and laser transmission[13] **(Figure 3)**. Care should be taken while manipulating the probe as improper handling or excessive bending can lead to fibre breakage, resulting in a loss of resolution or black spots on the display.

The ability to rotate the probe and shift its position allows for real-time alterations in the field

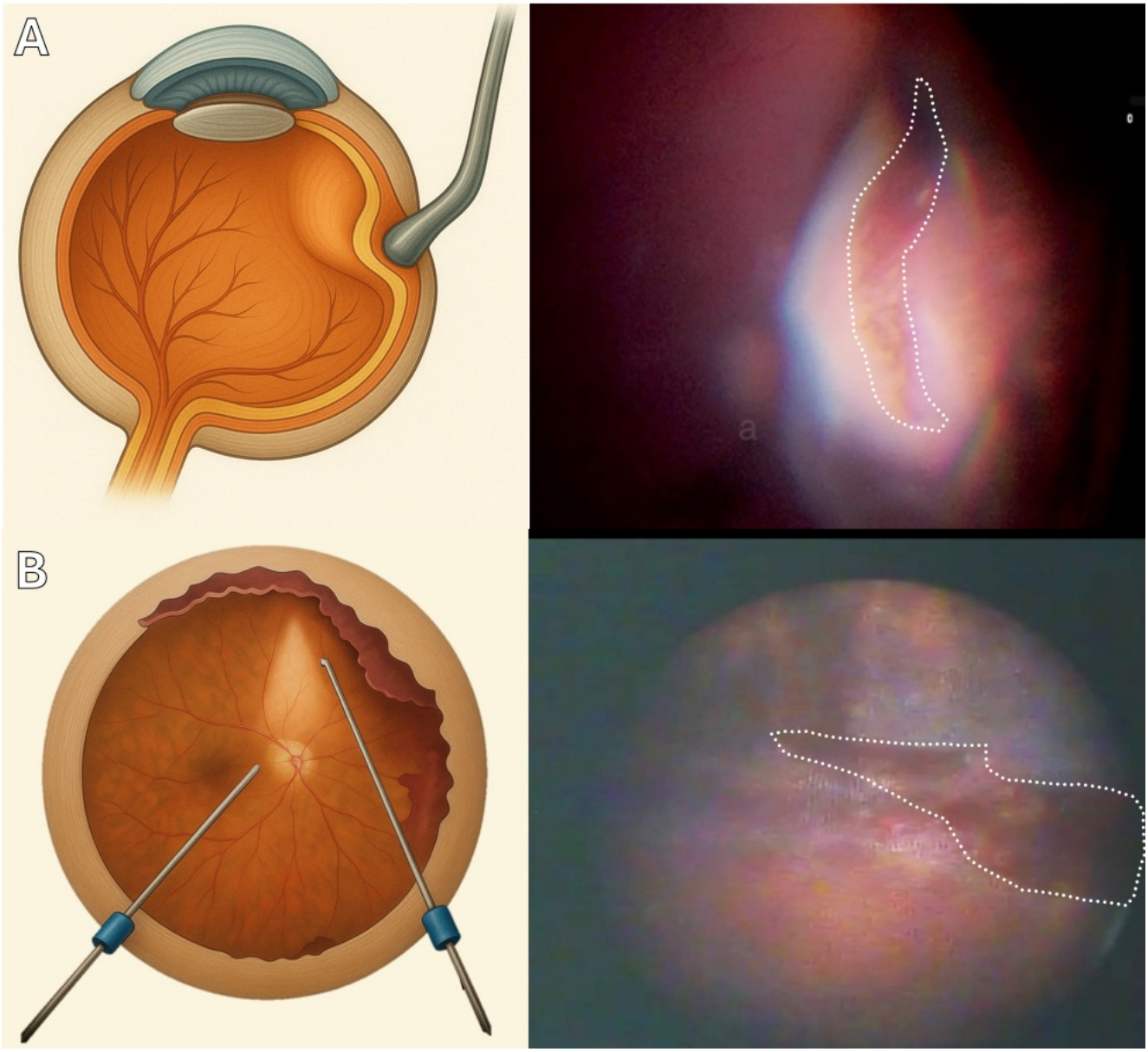

Figure 1. Comparison of the visualization of a large ora serrata break using a microscopic top down view with scleral depression (line A) versus an endoscopic view (line B). While the image at line A has a higher image resolution, scleral depression introduces structural distortions and prevents visualization of the vitreous and retroirideal structures anterior to the break. In contrast, line B demonstrates how endoscopy provides an undistorted view and enables more thorough shaving of the anterior vitreous base under direct visualization; *courtesy of Flavio A. Rezende, MD, PhD and Thiago Machado Nogueira, MD*

of view, enabling visualization of up to 90-140° at a time, depending on the calibre of the endoscope. Additionally, using two strategically positioned cannulas for small-gauge probes can provide a full 360° view.

Clinical Applications

Endoscopic vitrectomy serves two primary roles: endoscopy-guided PPV for eyes with anterior segment opacities where a top-down view with the microscope is not possible, and endoscopy-assisted PPV to enhance visualization of peripheral and retroirideal structures even in eyes with clear media.[14] This dual utility expands its indications significantly and enables earlier and more precise surgical intervention in complex cases **(Figure 5)**.

1. Anterior Segment Opacities:

In cases involving corneal edema, scarring, opacities, anterior chamber hemorrhage, or dense cataracts, endoscopic imaging provides direct visualization beyond opaque media. This approach eliminates the need for temporary or permanent keratoprosthesis or penetrating keratoplasty in situations where these interventions may be technically challenging or carry high risks. Endoscopy is particularly valuable in cases of severe fibrin formation, hyphema—which may be accompanied by corneal blood staining—and in procedures such as intraocular foreign body removal when conventional visualization is compromised. These advantages enable timely intervention, which is critical in urgent scenarios such as trauma, endophthalmitis, or retinal detachments with compromised anterior segment transparency.[2,5,15,16]

2. Ocular Trauma:

Endoscopy is invaluable for managing complex trauma involving IOFBs, retinal detachment, or endophthalmitis. In eyes with compromised corneas or anterior segments, endoscopy permits complete posterior segment evaluation and intervention. It also eliminates the need for scleral depression, which is contraindicated in cases of open-globe trauma.[4,11,17,18]

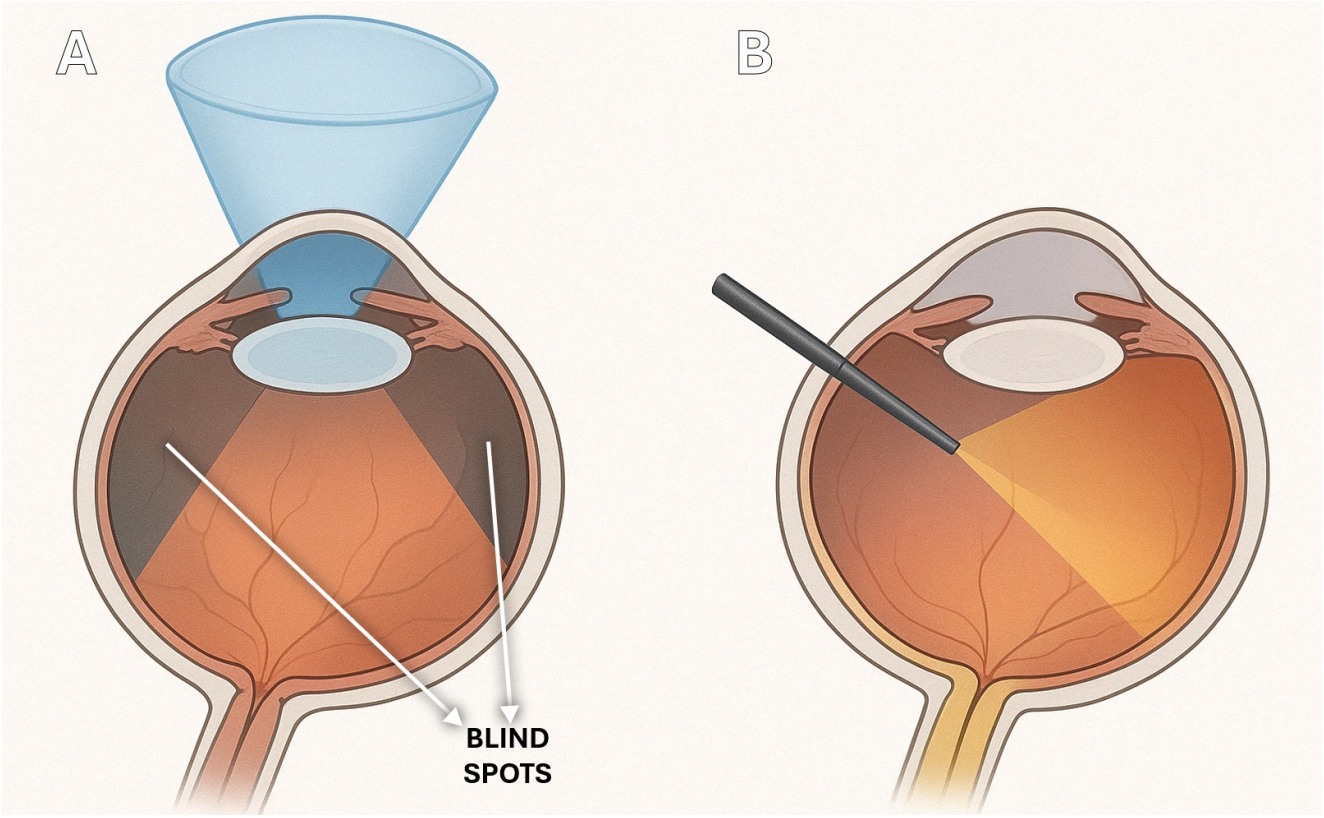

Figure 2. Comparison between the traditional top-down view using a surgical microscope (A) and the endoscopic view (B). Unlike the fixed microscopic perspective that obscures peripheral retroirideal structures in blind spots, endoscopy enables direct visualization of these otherwise inaccessible areas; *courtesy of Flavio A. Rezende, MD, PhD and Thiago Machado Nogueira, MD*

3. Retinal Detachment and Proliferative Vitreoretinopathy (PVR):

In cases of retinal detachments associated with anterior PVR, chronic hypotony, or ciliary body detachment, endoscopy enhances the identification and treatment of subtle pathology. It facilitates subretinal fluid drainage without posterior retinotomies and provides access to the anterior retina, vitreous base, ciliary body, and retroirideal space.[4,7,19-21]

4. Endophthalmitis:

Early vitrectomy in endophthalmitis improves outcomes, but dense media opacity can impede visualization. Endoscopy allows for timely removal of infectious material as well as visualization and assessment of posterior segment structures. This approach contributes to globe preservation and improved visual prognosis.[15,22]

5. Secondary Intraocular Lens (IOL) Fixation and IOL Complications:

Endoscopy enables accurate visualization of the ciliary sulcus and the assessment of the optic zone, haptics, and suture placement in scleral-fixated IOLs. By confirming optimal positioning, it minimizes complications such as IOL dislocation, hemorrhage, and uveitis-glaucoma-hyphema (UGH) syndrome. In postoperative evaluations, it aids in diagnosing and managing complications that are not visible through the standard microscope top-down view.[7,23]

Feature	Microscopy (Wide-angle Systems)	Endoscopy
Stereopsis	Present	Absent
Image Resolution	High (limited by surgeon's retina or camera resolution)	Variable; dependent on endoscope gauge and chip resolution
Field of View	Blind spots in retroirideal structures, partially compensated by scleral depression but prone to image deformations and lens border aberrations	90–140° at a time; 360° if two strategically positioned cannulas are used; independent of anterior segment clarity
Anterior Visulization	Limited to vitreous base	Extended up to iris, ciliary body, and retroirideal space
Access Through Opacities	Impaired by corneal/lens opacity or miosis	Unaffected by opacities or small pupils
Illumination	Transmitted through cornea and lens	Reflected light; coaxial illumination
Image Visualization	Direct through oculars or 3D monitor	On screen only; dissociation from surgeon's familiar line of sight with the microscope
Magnification	Optical zoom; may not enhance detail	Physical proximity allows enhanced detection of small lesions
Manipulation Axes	2 axes (horizontal and verticle)	3 axes (horizontal, vertical, rotational)
Learning Curve	Familiar to most vitreoretinal surgeons	Requires adaptation to 2D screen and lack of depth perception

Table 1. Comparing features of microscopy and endoscopy; *courtesy of Flavio A. Rezende, MD, PhD and Thiago Machado Nogueira, MD*

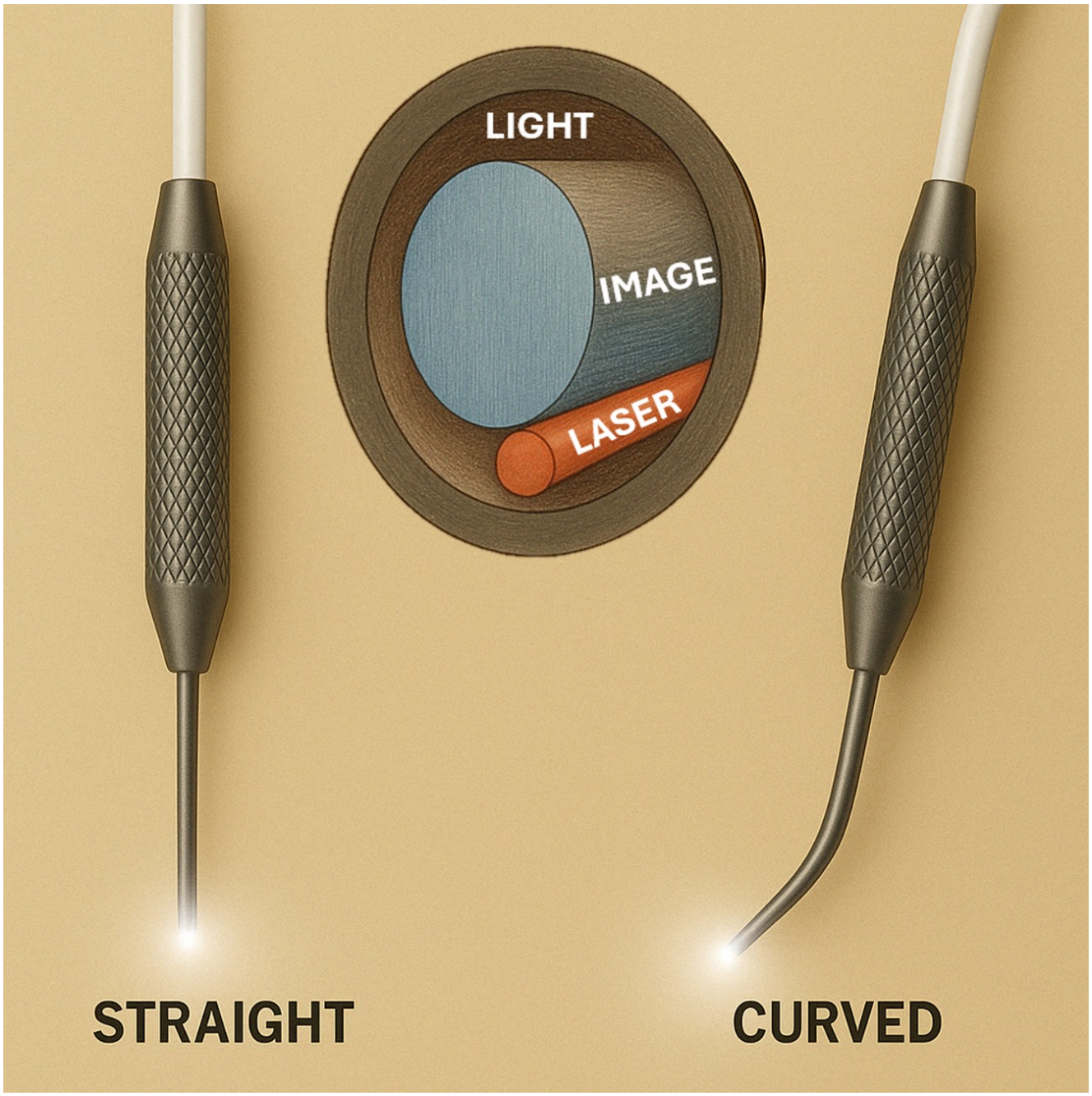

Figure 3. Endoscopic vitrectomy probes are available in straight and curved designs. Straight probes offer intuitive handling and simplified orientation, while curved probes enhance access to anterior structures that may be difficult to visualize in certain surgical contexts. Each probe incorporates dedicated fibre bundles for illumination, imaging, and laser delivery, enabling coaxial illumination/visualization and laser application regardless of corneal clarity or pupil size. When stationary, the probe provides a field of view ranging from 90° to 140°, depending on its calibre. Complete visualization of the posterior segment can be achieved by manipulating the probe and using two well-positioned cannulas for optimal access; *courtesy of Flavio A. Rezende, MD, PhD and Thiago Machado Nogueira, MD*

6. Glaucoma Surgery:

Endoscopy facilitates the placement of pars plana tube shunts by allowing a more complete shaving of the anterior vitreous and ensuring proper positioning of the implant through the pars plana. This reduces the risks of blockage and other postoperative complications.[24] It also enables comprehensive 360° endocyclophotocoagulation (ECP).[25] This method is superior to transpupillary approaches, which can only treat up to 9 clock hours of the ciliary body. It is particularly useful in refractory cases, including neovascular or pediatric glaucoma. In malignant glaucoma, it enhances visualization and dissection of the anterior hyaloid, guaranteeing the patency of the communication between the anterior and posterior segments with Irido-Zonulo-Hyaloido-Vitrectomy.

7. Pediatric Vitreoretinal Diseases:

Pediatric eyes, due to their small size and unique anatomy, present additional challenges. In conditions such as retinopathy of prematurity, persistent fetal vasculature, and familial exudative vitreoretinopathy, endoscopy improves tissue dissection and visualization near the lens and pars plicata.[8] This technique enhances surgical precision, reduces iatrogenic damage, and supports visual outcomes in otherwise inoperable cases.[8,9]

8. Subretinal Procedures:

Endoscopy permits precise membrane removal under the detached retina, avoiding the need for posterior retinotomies. This is particularly valuable in subretinal PVR cases where standard visualization is limited.[26]

9. Keratoprosthesis Planning and Management:

Preoperative endoscopy allows for the evaluation of the posterior segment before keratoprosthesis placement. Postoperatively, it

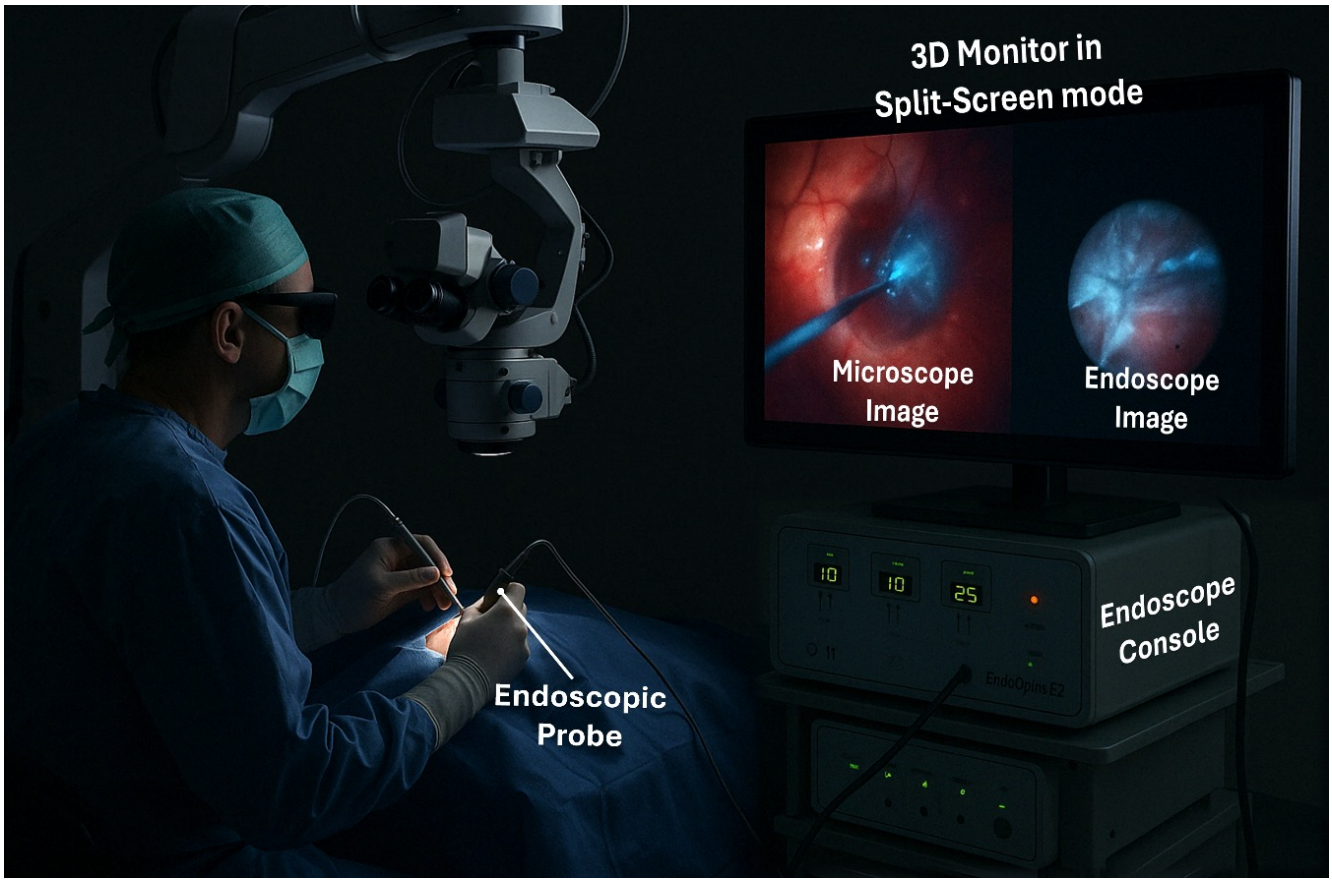

Figure 4. Set-up of an integrated endoscopic view within a three-dimensional (3D) visualization system. The split screen configuration enables a simultaneous display of both microscopic and endoscopic images, improving spatial orientation and eliminating the need to alternate between separate microscopes (or a 3D display) and endoscopy monitors. This configuration enhances ergonomics and provides greater comfort for the surgeon throughout the procedure; *courtesy of Flavio A. Rezende, MD, PhD and Thiago Machado Nogueira, MD*

supports interventions such as retinal detachment repair, endophthalmitis surgical treatment, retroprosthetic membranectomy, and ECP.[27,28]

10. Panretinal Photocoagulation (PRP):

PRP can be delivered through the pars plana using endoscopic visualization in ischemic retinopathies where standard views are obscured.[16] This method allows for complete peripheral treatment, potentially reducing recurrence or progression.

11. Sclerotomy-associated Complications:

Endoscopy allows for intraocular analysis of sclerotomy sites, which is useful for identifying vitreous and retinal incarceration as well as pinpointing the source of intraoperative or postoperative hemorrhages.[29]

12. Diagnostic Endoscopy:

When conventional imaging is inconclusive, diagnostic endoscopy provides direct intraocular visualization. This technique is useful in cases of trauma, opaque cornea, and preoperative planning for keratoplasty. It aids in surgical decision-making, prognostication, and patient counselling.[3,7,11]

Surgical Technique

Endoscopic vitrectomy typically complements standard PPV. Proper planning of trocar placement is essential to accommodate probe angulation and allow full quadrant access.[11]

Intraoperative technique involves dynamic manipulation of the endoscope, requiring adaptation to two-dimensional imaging without stereopsis. Surgeons must rely on visual depth cues and tactile feedback to infer spatial relationships.[29] Changes in probe orientation significantly alter the field of view, which may be unintuitive for those accustomed to the fixed top-down perspective of a microscope rather than the side-on view provided by endoscopy.[12]

While traditional endoscopy systems are costly and cumbersome, recent advances include portable units and modified high-resolution digital

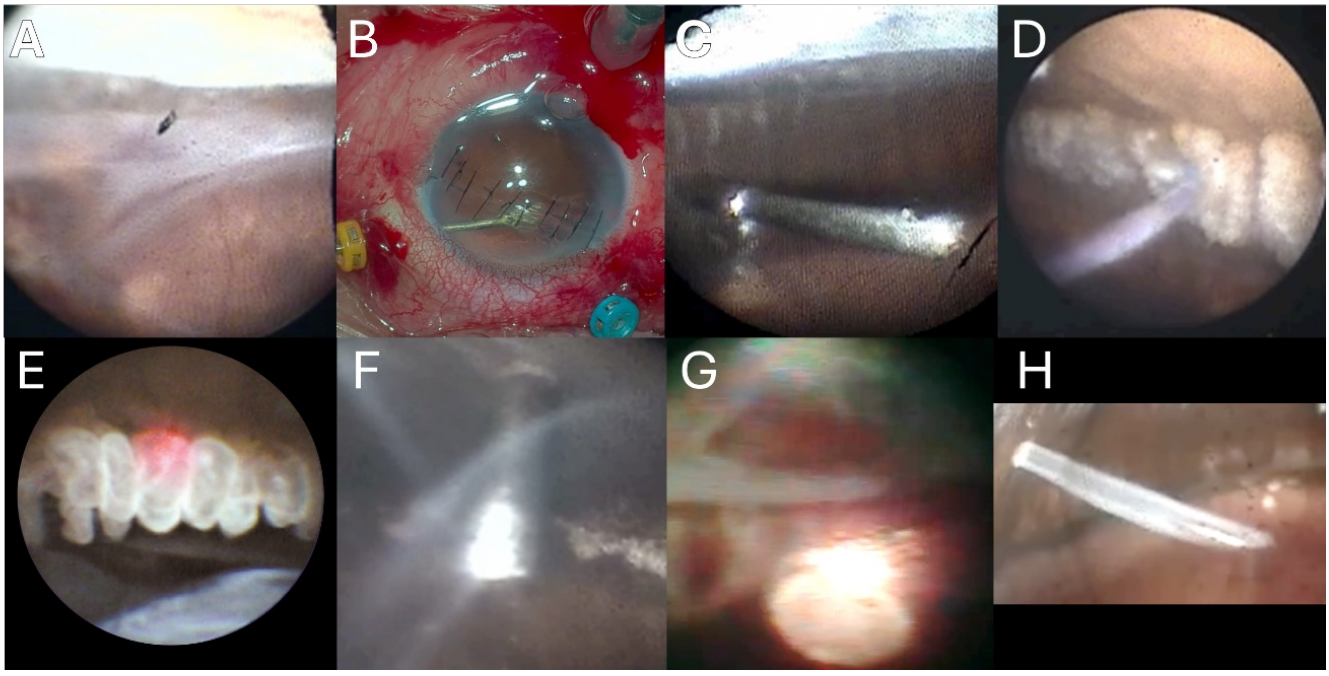

Figure 5. Representative surgical images illustrating key indications and applications of endoscopy. **A:** Dissection of anterior proliferative vitreoretinopathy (PVR); **B:** Vitrectomy in an eye with limited anterior segment transparency; **C:** Shaving of the retroirideal vitreous and anterior hyaloid. **D:** Evaluation of a scleral-fixated intraocular lens (IOL) - this image reveals a haptic piercing a ciliary process, which accounts for the recurrent postoperative vitreous hemorrhage; **E:** Endocyclophotocoagulation (ECP) of the ciliary processes; **F:** Identification of vitreous incarceration within a cannula; **G:** Confirmation of patency of the communication between anterior and posterior segments during Irido-Zonulo-Hyaloido-Vitrectomy for malignant glaucoma; **H:** Intraoperative positioning of a pars plana tube shunt; *courtesy of Flavio A. Rezende, MD, PhD and Thiago Machado Nogueira, MD*

cameras, expanding accessibility.[30] The integration of heads-up displays and digital overlays improves ergonomics, decreases learning curve length, and reduces physical strain during lengthy procedures.

Endoscopy enables high-precision manoeuvres such as dissection of anterior PVR,[20] identification of subtle peripheral breaks,[6] and direct delivery of endolaser photocoagulation or endodiathermy. It enhances safety during fluid-air exchange and facilitates secure tamponade, even in compromised eyes.[31]

Limitations and Challenges

Despite its advantages, endoscopic vitrectomy faces barriers that limit its widespread adoption. One significant challenge is cost and accessibility; acquisition and maintenance are expensive, limiting availability in many centres.[12] Additionally, there is a training deficit, as few training programs offer structured exposure to endoscopy, resulting in underutilization.[10]

The absence of stereopsis is also a limitation. The two-dimensional image requires adaptation to pseudostereopsis, increasing the learning curve.[18] Ergonomic fatigue also poses a challenge, as maintaining orientation and adjusting hand position increases surgeon fatigue, especially during lengthy cases.[32]

There are also trade-offs between resolution and field of view. Smaller-gauge probes provide less detailed images, a smaller field of view, and reduced illumination, while larger calibre probes are less manoeuvrable.[9] The need to operate the endoscope with one hand precludes the use of standard bimanual surgical techniques, further complicating the procedure.[11]

Postoperative visualization presents another challenge. In persistently opaque anterior segments, traditional fundus exams are not feasible, requiring ultrasonography or repeat endoscopy in the postoperative period.[7] Addressing these challenges requires ongoing development in miniaturization, three-dimensional visualization, and simulation-based training. Wider adoption may be facilitated by the development of standardized curricula and evidence-based protocols.

Future Directions

Advances in endoscopic vitrectomy are expected to enhance its usability and clinical integration. One notable development is the combination with three-dimensional visualization systems. Integrating endoscopic views into heads-up display systems improves the surgeon's spatial awareness and ergonomics by eliminating the need to alternate between separate monitors. Additionally, the colour filters available in these systems can enhance endoscopic visualization in a split-screen setting.[5]

Digital enhancements also play a crucial role in image quality. High-resolution microcameras and real-time contrast modulation improve image quality.[33]

Emerging technologies, including chip-on-tip designs,[2] proximity sensors,[34] depth-sensing technologies,[7] three-dimensional ocular endoscopy,[35] and robotic endoscope holders,[36] promise enhanced visualization.

Furthermore, dedicated training in vitreoretinal surgery fellowships would improve adoption and proficiency among new users.

As clinical familiarity grows and technology advances, endoscopy will evolve from a niche tool to a standard adjunct in complex cases.

Conclusion

Endoscopic vitrectomy represents a transformative approach in vitreoretinal surgery that extends visualization beyond the limits of traditional microscopy. Its ability to bypass opaque media and access retroirideal structures makes it extremely valuable in complex vitreoretinal conditions. While technical challenges remain, surgeons can adapt through structured training and experience.

By complementing wide-angle systems, endoscopy reduces surgical blind spots, enhances precision, and broadens the therapeutic reach. As technology advances and clinical evidence grows, endoscopy will play an increasingly central role in the modern vitreoretinal surgeon's armamentarium. It provides a different point of view that reshapes intraoperative decision-making and enhances patient outcomes.

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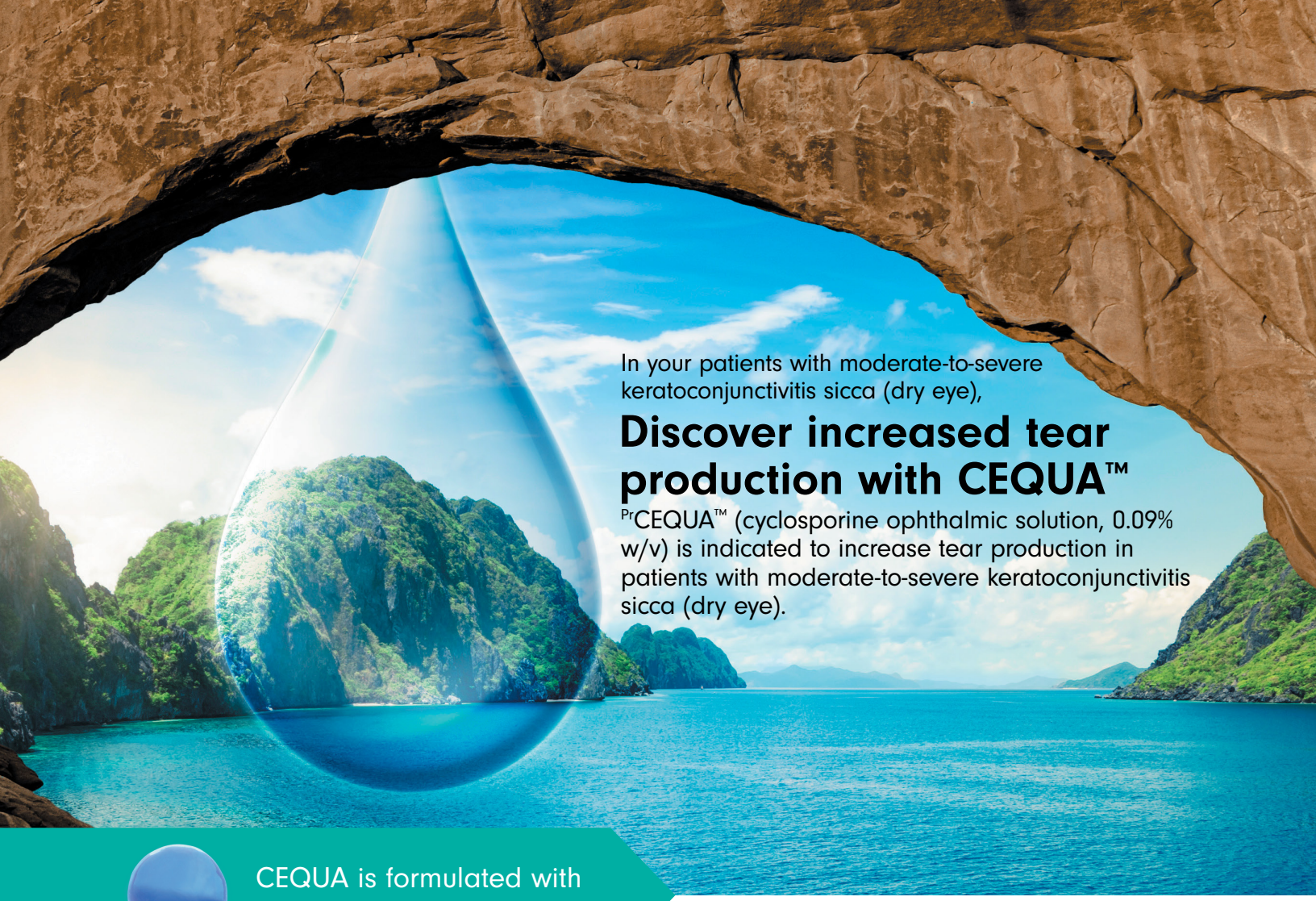

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*Clinical significance is unknown.

Clinical use:

Pediatrics (<18 years of age): The safety and effectiveness of CEQUA has not been established in pediatric patients; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (>65 years of age): No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

Contraindications:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container
- Patients with active or suspected ocular or peri-ocular infection
- Patients with ocular or peri-ocular malignancies or premalignant conditions

Relevant warnings and precautions:

- For topical ophthalmic use only
- Resolve existing or suspected ocular or peri-ocular infections before initiating CEQUA treatment. If an infection occurs during treatment, CEQUA should be temporarily withheld until the infection has been resolved
- Patients should be advised not to drive or use machines until their vision has cleared after CEQUA administration
- CEQUA has not been studied in patients with a history of *herpes keratitis,* end stage lacrimal gland disease, keratoconjunctivitis sicca (KCS) secondary to the destruction of conjunctival goblet cells such as occurs with Vitamin A deficiency, or scarring, such as occurs with cicatricial pemphigoid, alkali burns, Stevens-Johnson syndrome, trachoma, or irradiation
- Patients with severe keratitis should be carefully monitored
- Potential for eye injury and contamination
- CEQUA should not be administered while wearing contact lenses
- Local infections and malignancies: Regular monitoring of the eye(s) is recommended when CEQUA is used long term
- Hypersensitivity reactions
- The effect of CEQUA has not been studied in patients with renal or hepatic impairment
- CEQUA is not recommended during pregnancy unless the benefits outweigh the risks
- Caution should be exercised when CEQUA is administered in nursing women

For more infomation:

Please consult the Product Monograph at https://pdf.hres.ca/dpd_pm/00060038.PDF for important information relating to adverse reactions, interactions and dosing information, which have not been discussed in this piece. The Product Monograph is also available by calling our medical department at 1-866-840-1340.

REFERENCE: Current CEQUA™ Product Monograph, Sun Pharma Global FZE.

PM-CA-CQA-0031

Cequa™ (cyclosporine ophthalmic solution) 0.09%

SUN PHARMA

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Next-Generation Ophthalmology: How Artificial Intelligence Is Shaping the Future of Eye Care

Michelle Khan, MD, FRCSC

Introduction

When Canada hosted the inaugural "Artificial Intelligence, Digital Health, and the Eye" conference in April 2023, it quietly launched what has become a defining forum at the intersection of technology and vision science in the country. A year later, the conference found a new stage at the Royal Society of Medicine in London, drawing global attention. This was largely because the keynote address was delivered by Professor Geoffrey Hinton, co-recipient of the 2024 Nobel Prize in Physics, and widely regarded as one of the founding fathers of deep learning. As modern medicine continues to be shaped by artificial intelligence (AI), the tone is unmistakably clear: the future is not only digital, but also intelligent.

Few medical specialties are as naturally aligned with AI as ophthalmology. Its high-resolution imaging and quantitative data make ophthalmology particularly well-suited for the integration of AI technologies. Beyond automating image interpretation, AI now holds promise in risk stratification, disease progression modelling, and even in democratizing access to subspecialty-level diagnostics—advances that could meaningfully alter the delivery of eye care across the globe.

Significant strides have been achieved in applying both machine learning (ML) and deep learning (DL) algorithms to major ophthalmic diseases, including diabetic retinopathy, age-related macular degeneration, glaucoma, cataracts, and various corneal pathologies. The U.S. Food and Drug Administration (FDA) has approved several AI-based platforms for clinical use, many of which are showing tremendous potential. Large language model AI systems, such as Generative Pre-Training–Model 4 (better known as GPT-4 by OpenAI), have demonstrated the ability to either match or outperform human

ophthalmologists in diagnosing and treating various ophthalmic diseases.[1] This article aims to provide a comprehensive review of the role of AI in ophthalmology, with particular attention to current clinical applications, emerging innovations, and the challenges that lie ahead.

AI Applications in Ophthalmology

1. Diabetic Retinopathy

AI has achieved significant milestones in diabetic retinopathy (DR) screening. FDA-approved systems such as IDx-DR are enabling autonomous detection of referable DR from fundus photographs. In a 2024 study conducted by Abràmoff and colleagues, an AI system achieved 87.2% sensitivity and 90.7% specificity in detecting referable DR.[2] Beyond screening, AI is able to predict DR progression by analyzing longitudinal optical coherence tomography (OCT) data, enabling personalized monitoring intervals.[3] DL algorithms can analyze retinal images with high accuracy, and identify and grade the severity of DR, which allows efficient processing of large volumes of images. These algorithms can further identify microaneurysms, hemorrhages, and exudates with a sensitivity and specificity exceeding 85%. This reduces the dependence on manual grading and has the potential to expand access to screening in primary care settings.[4]

2. Glaucoma

AI offers promising solutions for cost-effective glaucoma screening through automated analysis of fundus and OCT images. AI systems can now detect glaucomatous optic neuropathy with high sensitivity and specificity. Unlike fundus imaging, OCT provides three-dimensional imaging that can detect depth-related structural changes in glaucoma. AI models trained on OCT images have exhibited superior accuracy compared to those trained on fundus images, performing comparably to experienced glaucoma specialists.[5] AI can also predict glaucoma progression by analyzing visual field data, allowing for earlier identification of disease progression than traditional methods. At the recent Heidelberg Engineering Symposium, experts highlighted AI's role in risk stratification, particularly for patients with normal-tension glaucoma, where traditional metrics often fail. These advancements in AI technology enhance early detection and monitoring of glaucoma, facilitating timely interventions and ultimately resulting in better patient outcomes.

3. Age-Related Macular Degeneration and Retinal Imaging

AI has several applications that can potentially transform the diagnosis and treatment of age-related macular degeneration (AMD). AI models are able to detect and predict the progression of AMD, effectively quantifying drusen volumes and geographic atrophy progression using OCT and fundus autofluorescence. DL models can classify disease severity into early, intermediate, and advanced stages with 94% accuracy, offering the potential to customize anti-vascular endothelial growth factor (VEGF) treatment protocols.[6] Generative adversarial networks (GANs), a type of ML model that uses two neural networks to compete against each other, can enhance image resolution, thus enabling the detection of nascent subretinal drusenoid deposits that predict late-stage AMD.[7] In addition, these models can accurately predict visual acuity response to treatment, which may considerably increase patient compliance. Lastly, DL AI models can effectively predict the conversion to geographic atrophy and suggest new biomarkers for AMD conversion.[7]

AI has also shown significant progress in diagnosing and staging retinopathy of prematurity (ROP). These systems are enhancing the efficiency and accuracy of ROP screening, thereby reducing the workload on clinicians and enabling timely interventions for these patients.[8]

4. Anterior Segment Applications

AI technology is showing growing utility in diagnosing and managing a range of ocular surface and corneal diseases. AI models trained on corneal topography, tomography, and anterior segment OCT can detect subclinical keratoconus (forme fruste) and classify disease severity with high accuracy, achieving 98% sensitivity in recent trials.[6] The grading of lens opacities, once a subjective clinical assessment, is now being automated through AI analyses of slit-lamp and fundus images, thereby streamlining cataract evaluations. More recently, smartphone-integrated AI platforms (such as CorneAI), have emerged, with the ability to distinguish between various corneal pathologies via simple slit-lamp photographs. This development holds particular promise in resource-limited settings. Beyond infection and ectasia, convolutional neural

networks have also shown success in recognizing subtle patterns associated with Fuchs' endothelial dystrophy, map-dot-fingerprint dystrophy, and Salzmann's nodular degeneration—potentially informing both medical therapy and surgical decision-making.[6,9]

5. Intraocular Surgery

Currently, AI applications in cataract and vitreoretinal surgery focus largely on surgical planning, real-time decision support, and postoperative outcome prediction. ML algorithms, trained on large datasets of biometric and intraoperative parameters, have demonstrated improved accuracy in intraocular lens power calculations. These algorithms outperform conventional formulas, particularly in eyes with atypical anatomy, such as those that have undergone post-refractive surgery or have high axial myopia.[10] In cataract surgery, AI-integrated platforms can predict the likelihood of intraoperative complications such as posterior capsular rupture based on preoperative imaging, and patient-specific variables.[11] In vitreoretinal surgery, AI is being explored for its potential in instrument tracking, surgical phase recognition, and microsurgical skill assessment, enabling objective analysis of surgical videos. This research is laying the exciting groundwork for intelligent robotic assistance and automated training feedback.

6. Telemedicine and Population Health

The COVID-19 pandemic served as a catalyst for the rapid adoption of AI in tele-ophthalmology, particularly in the realms of DR and ROP. At India's Aravind Eye Care System, one of the world's largest eye care networks, autonomous AI implementation has led to a significant reduction in screening costs while maintaining a diagnostic concordance rate of 92% compared to retina specialists.[12] Liu et al. assessed the cost-effectiveness and cost-utility of AI-driven screening for 5 major eye diseases in China, including DR, AMD, glaucoma, cataract, and refractive errors.[13] The study demonstrated that AI-supported telemedicine was the dominant strategy, providing superior cost-effectiveness in 90% of rural and 67% of urban regions. These findings underscore the economic and clinical viability of AI-based screening models, particularly in large-scale public health systems and underserved areas where access to subspecialty care is limited.

Challenges and Limitations

Despite its tremendous potential, the integration of AI into routine clinical ophthalmology faces several challenges. Concerns around model transparency, generalizability across diverse populations, ethical implementation, and regulatory oversight continue to slow widespread adoption.

A critical limitation lies in data heterogeneity and algorithmic bias. Most AI models are trained on datasets derived from high-income countries, which restricts their applicability to broader global populations. For instance, a 2024 study demonstrated that DR algorithms trained on Western cohorts significantly underperformed when applied to African populations, raising concerns about equity and reliability in global deployment.[14]

Generative AI and large language models, while holding great potential, have shown a susceptibility to errors, which introduces significant concerns about accuracy and accountability in clinical practice.

Even in regions where AI technologies have received regulatory approval, clinician skepticism remains a significant barrier. A 2025 study revealed that approximately 45% of ophthalmologists surveyed were unwilling to trust AI-generated recommendations.[15] Furthermore, many current electronic medical record systems are not designed for AI interoperability, which limits seamless usage.

Finally, there is a substantial gap in AI literacy among clinicians, which perpetuates the so-called "black box phenomenon"—wherein providers are hesitant to rely on models whose decision-making processes are not fully understood. This issue, combined with smaller and non-representative training datasets, discrepancies between research and clinical settings, and regulatory uncertainty, underscores the need for clinician education and transparent AI design before full-scale clinical integration can be achieved.

Future Directions

The future of ophthalmology lies in the evolution of multimodal AI systems. These advanced tools are capable of synthesizing complex datasets such as imaging, functional testing, genomics, and longitudinal health records to deliver care that is predictive, personalized, and preventive. AI models offering simultaneous

screening for multiple ocular conditions from a single imaging session are already demonstrating significant clinical utility, particularly in diseases such as glaucoma and AMD.

On the surgical front, augmented reality and AI-assisted navigation systems are poised to enhance intraoperative precision by improving tissue visualization and depth perception in real-time. Concurrently, advances in robotic microsurgery, powered by AI-driven feedback loops and real-time data fusion, suggest a future where semi-autonomous surgical systems augment both safety and efficiency in complex procedures.

The deployment of mobile and cloud-based AI platforms in pharmacies, community clinics, and underserved settings is democratizing access to expert-level diagnostics. As AI becomes more seamlessly integrated with electronic medical records and tele-ophthalmology infrastructure, its role in population-level screening, triage, and disease management will continue to expand.

While challenges around transparency, bias, regulations, and clinician trust remain, the convergence of AI and ophthalmology is undeniably transformative. The future will be shaped not only by technological breakthroughs, but also by our collective ability to implement them ethically, equitably, and intelligently. If realized responsibly, AI will not merely enhance eye care—it will redefine its reach, precision, and promise.

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Common Side Effects With Glaucoma Medications

Evan Michaelov, MD

Introduction

Glaucoma is a progressive optic neuropathy that affects more than 400 000 Canadians[1] and up to 111 million are expected to be afflicted with the disease worldwide by 2040.[2] Despite trends toward increasing utility of laser and surgical interventions for glaucoma treatment, topical medications remain a mainstay of treatment. These medications often comprise the initial treatment alongside selective laser trabeculoplasty (in open angle subtypes). Additionally, given the progressive nature of glaucoma, many patients who undergo laser or surgery treatments may eventually require the use of topical medications. Although glaucoma drops are generally accepted as safe and low risk for patients, each type carries its own side effect profiles and contraindications. No glaucoma drop is completely benign and can significantly affect patient wellbeing if not selected correctly. Therefore, it is important for ophthalmologists and eye care professionals, who will undoubtedly have numerous glaucoma patients in their care, to be aware of common side effects and contraindications associated with ocular anti-hypertensive agents. This article will outline the side effects and contraindications of the ocular anti-hypertensive agents currently available in Canada.

Prostaglandins

Prostaglandin analogs (PGAs) are often the first choice for the initiation of glaucoma therapy, largely due to their convenient once-daily dosing, superior efficacy, and infrequent side effects.[1] Although the exact mechanism of action is unknown, PGAs are believed to increase uveoscleral outflow, thereby reducing intraocular pressure (IOP). This class of medications typically achieves an IOP lowering in the range of 25-33%.

Conjunctival hyperemia is a common side effect of topical PGAs, occurring in approximately 15% of patients using latanoprost and up to 40% of those using bimatoprost (0.03% concentration).[3] However, if there is no concurrent discomfort or alternative cause of hyperemia, conjunctival hyperemia alone may be acceptable to the patient. It is important for the eye care provider to assess and determine the cause of hyperemia.

PGAs also induce changes in iris pigmentation and lash growth. While these changes are cosmetic in nature, they can be of significance to patients and should be discussed prior to treatment. Iris pigmentation changes are particularly common in patients with hazel or green irides and are least common in those with blue irides.[4] Iris colour changes tend to be permanent, even after cessation of the PGA.

Chronic use of PGAs can result in prostaglandin-associated periorbitopathy, which is characterized by symptoms such as ptosis, deepening of the lid sulcus, mild enophthalmos, and periorbital fat atrophy. These changes usually resolve with cessation of the PGA.

PGAs are relatively contraindicated in patients with a known history of herpetic keratouveitis due to the risk of reactivation. Although there was a belief that PGAs could potentiate cystoid macular edema (CME) and should be avoided in patients at higher risk of CME, recent studies have refuted this claim.[5]

Beta Blockers

Before the introduction of PGAs, beta adrenergic antagonists were the most commonly used topical medication for the treatment of glaucoma. These medications lower IOP by reducing aqueous production, generally achieving an IOP reduction in the range of 25-30%. They are generally prescribed to be taken twice daily but can usually be equally efficacious with once-daily dosing. When administered once-daily, they should be dosed in the morning as aqueous production is naturally lower over night, making the medication less efficacious during that time. Furthermore, morning dosing may reduce the incidence of nocturnal hypotension and may provide increased benefits for patients with normotensive glaucoma.[6] Most available beta blockers available for glaucoma are non-selective with the exception of betaxolol, which is β-1 selective, but less efficacious in reducing IOP. Patients taking systemic beta blockers may experience a reduced IOP-lowering effect. Additionally, beta blockers have been noted to have a tachyphylactic effect, where efficacy decreases with time due to the upregulation of the target receptor of the drug.

Beta blocker drops can cause blurring of vision and discomfort, however, they are usually well tolerated. Patients with myasthenia gravis may experience a worsening of their ocular symptoms when using beta blocker drops. Additionally, corneal anesthesia has been reported with the use of beta blockers which can lead to neurotrophic sequalae affecting the cornea. Beta blockers may also cause reduced exercise tolerance, decreased libido, and depression.

Contraindications: Most of the issues patients experience with beta blockers stem from their systemic effects. Beta blockers are contraindicated in those with obstructive lung diseases such as asthma and chronic obstructive pulmonary disease, as their systemic effects on the smooth muscle in the lung can cause severe bronchospasm. β-1 selective drops (betaxolol) may reduce the risk of these adverse effects, but they can still occur and should be used with caution. Patients with bradycardia or heart block should avoid this agent as it can lead to an exacerbation of their condition. Individuals with diabetes should be advised that these agents can mask symptoms of hypoglycemia, which can predispose them to hypoglycemic crises. Lastly, rapid withdrawal of the agent can trigger symptoms of hyperthyroidism.

Carbonic Anhydrase Inhibitors

Carbonic Anhydrase inhibitors (CAIs) are available in both topical and oral forms. While the United States Food and Drug Administration (FDA) has approved topical administration for 3 times daily dosing, most physicians prescribe them twice daily. This class includes 2 medications: brinzolamide, introduced in 1998, and dorzolamide, introduced in 1995. Overall, this class of medications are slightly less potent than other topical medications, typically reducing IOP by approximately 15-20%.

Both classes of CAIs share similar side effect profiles when used as topical agents. These side effects include conjunctival injection, punctate keratopathy, blurring of vision, and pain on administration. Pain tends to be worse with dorzolamide, due to its low pH, while blurring of vision tends to be worse with brinzolamide, because it is a suspension. Topical CAIs should be avoided in patients with endothelial dysfunction, as carbonic anhydrase is an important component in endothelial pump function.[7] If using CAIs is necessary, patients should be frequently asked about any vision changes consistent with corneal edema, and pachymetry should be monitored.

Systemic Carbonic Anhydrase Inhibitors

Oral CAIs are potent medications for reducing IOP, however, they carry more substantial systemic side effects. Available options include acetazolamide and methazolamide. Common side effects include alterations in taste, especially with carbonated beverages, paresthesia in the fingers and toes, and general malaise. Due to their side effects, these oral agents are usually reserved only for maintaining adequate IOP while awaiting surgery, or for patients who are not suitable candidates for surgical intervention. Dosing should be reduced to the lowest tolerated level that maintains an adequate IOP.

Both agents result in potassium excretion, thus, patients should be monitored for hypokalemia, especially if they are also taking other potassium-wasting medications such as thiazide diuretics. Health care providers will frequently recommend increasing the patient's potassium intake while taking these medications.

Rarely, patients may develop aplastic anemia. They should be advised to consult their primary care physician for blood work if they exhibit signs of such, including petechia and fever.

Patients with chronic kidney disease, or those on dialysis, will require adjusted dosing of CAIs. Patients with hepatic disease should avoid oral CAIs due to the risk of hepatic encephalopathy. Before starting these medications, patients should be screened for sickle cell disease, as these medications may induce a sickle cell crisis.

Allergic reactions from CAIs in those with sulfa allergies are rare and should generally be avoided only in patients with a documented history of anaphylaxis to sulfa drugs.[8] However, CAIs are a known risk for Steven-Johnson Syndrome/Toxic epidermal necrolysis spectrum.

Finally, patients taking CAIs are at risk of developing nephrolithiasis. They should be advised to hydrate adequately to reduce this risk.

Alpha-Agonists

Alpha-Adrenergic agonists were previously available in both non-selective forms (epinephrine, dipivefrin), and alpha-2 selective forms (brimonidine, apraclonidine). the non-selective forms are no longer in use due to their significant side effect profiles. Alpha-2 selective agonists (α2A) can lower IOP by approximately 20-30% and are typically dosed either three times daily, or more frequently, twice daily. These α2A agents cause conjunctival vasoconstriction, and low concentration forms have been used for reducing vascularity for cosmesis or certain conjunctival-based procedures.[9]

The most common adverse effect of α2A agents is ocular allergy, which usually manifests as a follicular response and/or blepharodermatitis. Among topical glaucoma drops in this class, allergy rates are amongst the highest, with brimonidine causing allergic reactions in approximately 15% of patients after 1 year of use, and the incidence rates increase with continued usage.[10] Apraclonidine has higher allergy rates than brimonidine and is primarily used only in the prophylactic setting during laser procedures. Although alternative formulations with purite preservatives reduce these allergy rates, they remain elevated compared to other topical options.

Common adverse effects of α2A agents include dry mouth, lid retraction, and somnolence. Additionally, apraclonodine may cause mydriasis, whereas brimonidine may cause miosis.

Rarely, brimonidine treatment can cause granulomatous anterior uveitis. This reaction need-not occur immediately after starting the topical agent. It is important to consider discontinuing brimonidine use in glaucoma patients who present with new anterior uveitis.[11]

Alpha agonists are strictly contraindicated in children under the age of 2, as they may cause respiratory distress, hypotension, and central nervous system depression. Even in children older than 2 years, these medications should still be used with caution. Brimonidine is the only topical glaucoma drop that was previously classified under FDA category B for pregnancy, indicating it is presumed safe based on animal studies. It is considered the first-line treatment for pregnant patients. Patients taking tricyclic antidepressants and monoamine oxidase inhibitors should avoid α2A agents due to the risk of systemic hypotension, although this risk appears to be mostly theoretical.

Miotics

Miotics, once widely used for treating glaucoma for over 100 years, are now rarely used. The most common miotic is pilocarpine, a direct cholinergic agonist. Due to its numerous adverse effects and the need for frequent dosing (three to four times daily), its use has been relegated to niche scenarios including chronic angle closure status-post laser peripheral

iridotomy and aphakic glaucoma. IOP reduction with pilocarpine ranges from 15-25%.

Pilocarpine results in increased tension on the trabecular meshwork and associated structures and increased outflow due to contraction of the longitudinal ciliary muscle fibres. This action also causes anteriorization of the lens-iris diaphragm, which can lead to multiple consequences, including an increased risk of angle closure in phakic individuals (via increased pupil block), induced myopia, and head or brow aches due to ciliary muscle spasm. This effect may also account for the increased rates of retinal tears and detachments observed with pilocarpine use.[12] Therefore, patients should undergo a peripheral retinal exam prior to starting this medication.

Pilocarpine has also been shown to be cataractogenic, and its miotic effects can impact night vision and increase the risk of posterior synechiae formation. Additionally, pilocarpine can compromise the blood-aqueous barrier, making it unadvisable for use in uveitic glaucoma.

Systemically, pilocarpine use can result in increased cholinergic activity, which can include symptoms such as salivation, lacrimation, and abdominal pain.

Other Considerations of Topical Therapy

Despite the unique side effect profiles of each topical class, all drops are capable of irritation and discomfort for patients. The ongoing burden of using drops and the chronic nature of glaucoma treatment can be disconcerting for patients. In addition, physical constraints, which are common among a large population of glaucoma patients, can make the physical use of drops difficult, and can lead to poor adherence with treatment. Given these concerns, it is no surprise that glaucoma patients often prioritize freedom from, or reduction of, the use of drops.[13] As such, every effort should be made to reduce the use of drops. The LiGHT trial has demonstrated the efficacy of selective laser trabeculoplasty in both primary treatment and treatment escalation, and it should be used as appropriate.[14] When escalating medical treatment, it is important to have a good understanding of the available fixed combination drops to limit overall drop burden. Ideally, patients should be able to achieve maximum medical therapy with only two drops.

When glaucoma patients taking topical agents are ready for cataract surgery, it is important to consider planning additional minimally invasive glaucoma surgery. This approach can help minimize the drop burden and provide a greater buffer before considering more invasive filtering surgery.

When patients experience multiple drop intolerances, efforts should be made to offer preservative-free or alternative drops. Otherwise, optimizing the ocular surface using the standard dry eye management algorithm can sometimes improve tolerance.

Lastly, patients who are new to drops should be instructed on proper drop use techniques. Instruction on punctal occlusion may help prevent systemic absorption.

In conclusion, although topical medications are vital for glaucoma management, their use is not benign. It is important for eye care professionals to have an expert understanding of the available options and their adverse effects to ensure optimal patient care.

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The Evolution of Endothelial Therapeutics

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Introduction

Corneal endothelial diseases comprise a spectrum of conditions that critically affect the health and transparency of the cornea, posing unique challenges for ophthalmologists. The most prevalent among these is Fuchs' endothelial corneal dystrophy (FECD), which accounts for approximately 39% of all corneal transplants globally.[1] Bullous keratopathy (BK) can affect the entire cornea, leading to painful blisters that may become infected. Other rarer pathologies, such as iridocorneal endothelial syndrome, posterior polymorphous corneal dystrophy, and congenital hereditary endothelial dystrophy, present unique diagnostic and therapeutic challenges. Additionally, graft failure remains a notable indication for treatment. High-risk cases experience failure rates exceeding 35% within 3 years, with endothelial rejection accounting for half of the cases.[2] Corneal transplants have been considered the gold standard for decades, with advancements in surgical techniques leading to shorter operating times, faster visual recovery, and improved outcomes. However, the growing global shortage of transplant-grade donor tissue further complicates treatment, underscoring the urgent need for innovative approaches such as genetic and cell-based therapies.

Historical Review of Treatment

Penetrating Keratoplasty

For decades, penetrating keratoplasty (PK) was the mainstay of surgical treatment for corneal endothelial disease. However, postoperative complications can be significant, ranging from suture-related issues, delayed wound rupture, and corneal transplant failure. Moreover, surgically induced astigmatism is an important consideration for these patients. Those with bilateral disease often experience a prolonged waiting period between surgical intervention in each eye given the lengthy visual recovery time after PK. Given these disadvantages, there has been much interest in surgical methodologies that could focus solely on replacing the endothelium.

Endothelial Keratoplasty

The most significant evolution in therapy for endothelial diseases over the past 25 years has been the transition from full-thickness PK to selective transplantation of the endothelial layer. The origins of posterior lamellar keratoplasty date back to the 1950s, and in 1998, an intrastromal approach was proposed.[4] Although not widely adopted due to its surgical complexity, an era of innovation in endothelial keratoplasty (EK) techniques followed. The subsequent adaptation, deep lamellar endothelial keratoplasty (DLEK), integrated the use of viscoelastic to stabilize the anterior chamber amongst other modifications.[5] This was followed by Descemet-stripping endothelial keratoplasty (DSEK) and later Descemet-membrane endothelial keratoplasty (DMEK), which solidified EK as the treatment of choice for endothelial disease.[6]

DSEK involves replacing the host endothelium with a donor graft of endothelial and stromal tissue. Descemet stripping automated endothelial keratoplasty (DSAEK) is a subsequent advancement that includes the use of a microkeratome to cut the donor tissue. Compared to PK, DSAEK consistently results in less astigmatism, better wound stability, and faster visual recovery.[7] In DMEK, only the endothelium and its carrier Descemet's membrane are replaced with donor tissue, resulting in a much thinner graft. Both DSAEK and DMEK require removal of the host endothelium via a procedure called descemetorhexis, which can be achieved either manually or, less frequently, with a femto-second laser.[8]

In most countries with ready access to tissue and the ability to navigate a surgical learning curve, a shift toward DMEK has been observed for the majority of endothelial grafts.[9,10] Indeed, DMEK has become the gold standard for treating endothelial failure, with faster visual recovery, higher rates of 20/20 acuity, and the lowest rates of rejection.[11] Over a 10-year study period, DMEK showed the lowest median endothelial cell loss (63%), followed by DSEAK (68%), then PK (76%). Similarly, in terms of graft survival, a large series found that the cumulative risk of graft failure over 10 years was lowest with DMEK, followed by DSAEK, then PK.[7]

DMEK surgery presents technical challenges related to graft manipulation, particularly in the absence of an iris scaffold or deep chamber, as well as having a higher rebubbling rate. An uncommon but important intraoperative complication is fibrin release from the iris, which may have deleterious effects on endothelial corneal dystrophy (ECD) and graft survival. Anticoagulant use has been implicated as a risk factor alongside surgical trauma to vascular tissues and prolonged surgical manoeuvres. To mitigate this issue, strategies such as using heparin in the balanced salt solution infusion or tissue plasminogen activator (tPA), borrowed from veterinary and pediatric ophthalmic surgery, are being studied for their potential benefits.[12]

Finally, newer techniques for tissue preparation have emerged to address the technical challenges of DMEK surgeries by using DSAEK-like tissue preparation methods. In ultrathin-DSAEK (UT-DSAEK), donor grafts of approximately <110–100 µm thickness are transplanted, which are thinner than the traditional DSAEK's 150 µm and thicker than DMEK's average 10–15 µm thickness. UT-DSAEK displayed superior visual acuity outcomes compared to DSAEK in a large case series and randomized controlled trial without increasing the risk of graft detachment.[14] The term "nanothin" DSAEK (NT-DSAEK) is used to describe grafts achieving a thickness of ≤50 µm, but more studies are needed to evaluate the benefits of this technique.[15]

Descemet-Stripping Only

Descemet-stripping only (DSO), also known as Descemetorhexis Without Endothelial Keratoplasty (DWEK), has emerged as a surgical option for select cases of FECD. The primary indication for DSO is the presence of symptomatic central guttae and a clear peripheral cornea with an ECD >1000 cells/mm^2 (if measurable).[16] In DSO, the diseased endothelium and underlying Descemet's membrane are removed without subsequent transplantation **(Figure 1)**. The proposed mechanism for central corneal clearing is corneal endothelial cell (CEC) migration from the periphery to repopulate the endothelium. As a transplant-free approach, DSO avoids the surgical challenges associated with EK, including intracameral gas or air management, graft attachment complications, and rejection. However, this intervention has limitations, including prolonged visual recovery, and the possibility of subsequent surgeries.[17]

Originally described by Paufique in 1955, DSO has undergone a modern renaissance.[18] Recent studies have shown promising but somewhat unpredictable early results. While some cases have required subsequent EK, others have demonstrated complete resolution of corneal edema with improvement in best corrected visual acuity (BCVA) for reasons that were initially unclear.[19]

Recently, research in this area has shifted to investigate surgical factors that contribute to successful corneal clearance following DSO. Laboratory studies and medium-sized clinical trials have confirmed that surgical factors including descemetorhexis size and technique may contribute to differences in outcomes following DSO.[16] It is now accepted that limiting the descemetorhexis size to less than 5 mm, employing a peeling rather than scoring technique, and the addition of topical Rho-kinase (ROCK) inhibitors are proven strategies to improve the likelihood of DSO success, which now exceeds 90%.[17,20]

Emerging Therapies

Corneal transplantation remains the sole effective treatment for FECD. Nevertheless, modern EK techniques are not without complications. They are associated with a 28.8% allograft detachment rate and a 1.7% rate of primary graft failure during the immediate postoperative period, often requiring additional surgical interventions.[21] Long-term outcomes reveal graft failure rates of 3.8–5% at 5 years in specialized, single-centre settings. Furthermore, nearly 25% of patients develop glaucoma following EK, necessitating further medical or surgical management.[22] Globally, the limited availability of tertiary-care corneal transplant surgeons, along

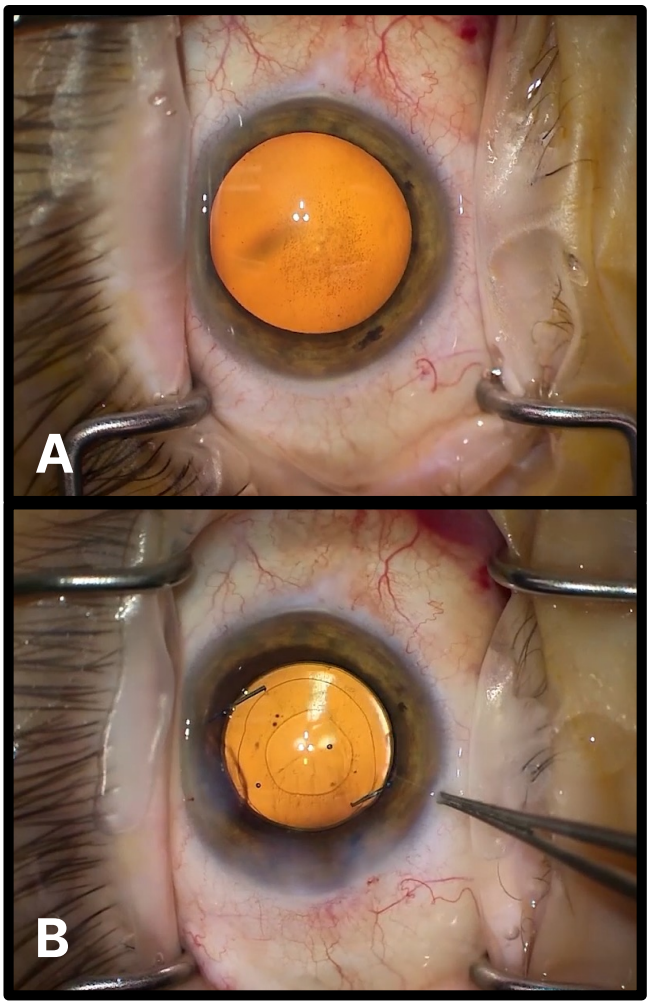

Figure 1. Surgeon's view of Descemet-stripping only (DSO) combined with phacoemulsification. **(A)** Preoperative view with eyelid speculum in place; **(B)** Postoperative view demonstrating the completed larger capsulorhexis and smaller descemetorhexis, with a 3-piece lens in the bag; *courtesy of Greg Moloney, MBBS (Hons), BSc(Med), MMed, FRANZCO, FRCSC, Antoine Sylvestre-Bouchard, MD, MSc., and Mary Holdsworth, MD, BSc, MScPH*

with insufficient donor tissue and eye banking infrastructure, restricts the accessibility of EK, emphasizing the urgent need for innovative treatment alternatives **(Table 1)**.

ROCK Inhibitors

Rho-associated coiled-coil containing protein kinases (ROCKs) are involved in cytoskeleton organization, cell migration, cell-cell adhesion, proliferation, cell cycle control, and apoptosis. ROCK inhibitors, by extension, have been shown to promote cell adhesion, inhibit apoptosis, and increase proliferation of CECs.[23] Based on these promising studies, the use of topical and injectable ROCK inhibitors has increased in recent years. For instance, topical Y-27632 and ripasudil have been shown to promote corneal endothelial wound healing and improve corneal edema in BK and FECD patients. Additionally, both Y-27632 and ripasudil have been successfully applied as salvage agents in cases of DWEK where the cornea failed to clear.[16] Most recently, a review of the role of ROCK inhibitors in corneal disease found that Y-27632, ripasudil, and netarsudil were all beneficial in promoting endothelial healing.[24] The primary mechanism of benefit appears to be the accelerated closure of endothelial defects, with well-demonstrated anti-apoptotic effects as well.[23]

Tissue-Engineered Grafts and Injected Cell Suspensions

With the global corneal donor shortage, there is a strong incentive to explore technologies that not only enhance but also replicate and/or replace the corneal endothelium. This can be achieved by leveraging tissue engineering modalities, such as Tissue-Engineered Endothelial Keratoplasty (TE-EK), and the injection of cell suspensions of cultured human CECs. Cultivating human CECs presents unique challenges, particularly to do with a low proliferative potential, rapid cellular senescence, and a tendency to undergo endothelial-to-mesenchymal transition. Fundamentally, TE-EK involves seeding human CECs onto a scaffold carrier, with various types of scaffolds having been investigated. The resulting endothelial sheet is then transplanted into the recipient's eye in a fashion similar to DSAEK. To date, several studies using animal transplantation models have shown that these endothelial sheets are functional in vivo, with similar morphology to native corneal endothelium.[25,26] Research groups have now progressed to human trials investigating TE-EK for conditions such as FECD or BK.

Studies investigating the delivery of cultured human CECs as a cell suspension have produced promising results, showing the formation of an endothelial monolayer and functional corneal endothelium.[27] The addition of ROCK inhibitors in these studies produced superior outcomes, presumably by enhancing adhesion and cell engraftment. A landmark clinical trial of patients with BK demonstrated that descemetorhexis followed by direct injection of human CECs and ROCK inhibitor, led to improved ECD in all 11 treated eyes. Improvements in BCVA and central corneal thickness were also reported

Contemporary		Emerging	
Penetrating Keratoplasty		**Pharmacologic Therapies**	ROCK inhibitors Antioxidants Fibroblast Growth Factor
Endothelial Keratoplasty		**Cell-Based Therapies**	Tissue-Engineered EK Cell Suspension Injections
DMEK			
DSAEK	UT-DSAEK NT-DSAEK	**Genetic Therapies**	Antisense oligonucleotides CRISPR
DSO			

Table 1. The Evolution of Endothelial Therapeuthic Options; *courtesy of Greg Moloney, MBBS (Hons), BSc(Med), MMed, FRANZCO, FRCSC, Antoine Sylvestre-Bouchard, MD, MSc., and Mary Holdsworth, MD, BSc, MScPH*

Abbreviations: DMEK: Descemet-membrane endothelial keratoplasty; **DSAEK:** Descemet stripping automated endothelial keratoplasty; **DSO:** Descemet-stripping only; **EK:** endothelial keratoplasty; **NT-DSAEK:** nanothin-DSAEK; **ROCK:** Rho-associated coiled-coil containing protein kinases; **UT-DSAEK:** ultrathin-DSAEK

in most eyes. Importantly, there were no major complications reported, and the improvements in corneal clearance and BCVA were sustained beyond 3 years in most cases.[28]

Antisense Oligonucleotides

Antisense oligonucleotides (ASOs) represent a promising avenue for the treatment of FECD with underlying trinucleotide repeat mutations. These short, synthetic, single-stranded oligodeoxynucleotides exert their effects by modifying RNA activity, enabling the reduction, restoration, or alteration of protein expression. Recent advancements in ASO pharmacology have accelerated their clinical translation, with two ASO therapies already approved by the US Food and Drug Administration (FDA) for conditions such as Duchenne muscular dystrophy and spinal muscular atrophy.[29]

The potential for treating FECD has been transformed by the discovery that expansions at the intronic CTG18.1 triplet repeat polymorphism of *TCF4* (MIM 602272) account for 70% of FECD cases in the United States. This finding establishes FECD as the most common repeat expansion disorder in humans.[30] *TCF4* expansions of greater than 40 CTG repeats confer a significant risk for developing FECD. In FECD endothelial tissue, expanded CUG-repeat RNA transcripts accumulate as nuclear foci that can be visualized by fluorescent in-situ hybridization. These nuclear foci ultimately sequester splicing factors and impair the splicing process.[31]

Subsequently, ASOs targeting this CTG18.1 repeat expansion in *TCF4* have been designed and investigated with results suggesting reduced RNA toxicity.[30] However, further application of ASOs in the clinic requires optimization of ASO delivery, target engagement, and safety profiles.[29] Current data suggests that in vivo delivery of ASOs to corneal tissue through intraocular injection (intracameral or intravitreal) is a feasible and effective method for regulating gene expression.

CRISPR

As our understanding of genetic mutations in corneal endothelial disease has expanded, the possibility of genome editing with CRISPR/Cas9 to target known mutations has surfaced. CRISPR/Cas9-mediated genome editing has been described in cultured human CECs and in murine models with *Col8a2* missense mutations. To date, no studies have demonstrated gene editing of the more common CTG repeats in *TCF4*. While there is enormous therapeutic potential, including the possible prevention of corneal endothelial disease

pathogenesis, challenges include the delivery method, delivery vector choice, and specific targeting.[32]

Antioxidants

Although FECD is a complex disease with several different primary mechanisms involved, secondary mitochondrial dysfunction and mitophagy play a central role in the decline of endothelial cell viability during the progression of this disease. The rationale behind antioxidant therapies rests on the premise that the oxidative response pathways are dysfunctional in patients with endothelial disease. Oxidative stress leads to dysregulated apoptosis of CECs. By targeting this dysfunctional response with free radical scavengers to mitigate the accumulation of reactive oxygen species, the aim is to improve the survival of CECs.[33]

FECD pathogenesis is also linked to environmental ultraviolet A (UVA) exposure. UVA exposure contributes to iron-mediated lipid peroxidation (ferroptosis) and CEC death in FECD. Experimental evidence shows that both iron chelation and anti-ferroptosis antioxidant treatments can prevent cell death in FECD cell cultures. Solubilized ubiquinol, the active form of Coenzyme Q10, has been shown to prevent cell death caused by RSL3-induced ferroptosis, suggesting a potential role for anti-ferroptosis therapies in FECD.[34]

Conclusion

Over the past few decades, corneal endothelial treatments have significantly evolved, transitioning from advancements in partial thickness keratoplasty to tissue-sparing, transplant-free innovations. While challenges such as global donor tissue shortages and postoperative complications persist, developments in cell-based therapies, tissue engineering, and molecular approaches are expanding treatment options and accessibility. If recent history is any indication, ongoing research will continue to propel endothelial disease treatment forward, restoring vision and improving quality of life.

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Surgical Pearls for Pterygium Surgery

Randall Ulate, MD

Introduction

Pterygium, a common ocular surface disorder, manifests as a wing-shaped degenerative fibrovascular benign growth characterized by the fibrovascular proliferation of conjunctival tissue onto the cornea **(Figure 1)**. This condition often results from prolonged exposure to ultraviolet light, dry eye conditions, or chronic irritation. On histopathology, there is classically elastotic degeneration of the conjunctival stroma with overgrowth of blood vessels and fibrous tissue, i.e., a fibro-proliferative reaction.[1,2] While small and asymptomatic lesions may be managed conservatively, surgical excision becomes necessary when the lesion threatens vision, causes significant discomfort, or results in cosmetic concerns. A pterygium with documented growth that extends toward the visual axis should be removed before it reaches the central cornea. However, due to its high recurrence rate and variability in presentation, surgical management of pterygium requires attention to detail and a thorough understanding of optimal techniques.

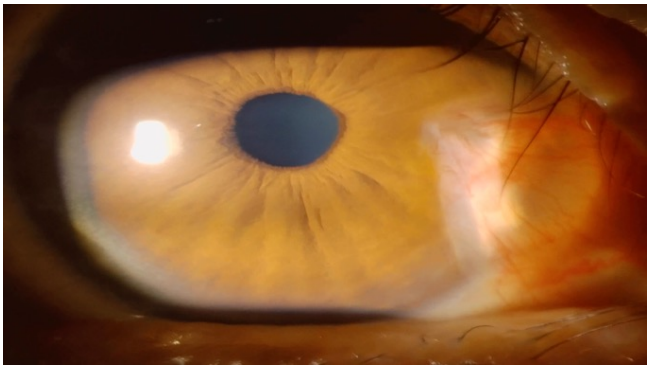

Figure 1. Pterygium. Wing shaped fibrovascular tissue at the nasal limbus and cornea; *courtesy of Randall Ulate, MD*

Pterygium Surgical Techniques

Over the decades, pterygium surgery has seen significant advancements, with multiple techniques being developed to reduce recurrence and improve outcomes. Each technique offers its own set of benefits and risks, and the selection often depends on the size and type of the pterygium, the surgeon's preference, and the available resources. The goal of pterygium surgery is to obtain good visual acuity and cosmetic

appearance, avoid complications, and achieve a low recurrence rate.[3,4]

Bare Sclera Technique

The pterygium is excised, leaving the underlying sclera exposed without any tissue graft or coverage. This technique has the advantage of being simple and quick to perform and requires minimal instrumentation.[5] However, it comes with several disadvantages. The recurrence rate is high, ranging from 30–80%, and the exposed sclera may scar or become inflamed, leading to poor cosmetic results. Therefore, this technique should not be used as a standalone technique due to its high recurrence rate.

Beta Irradiation (Beta Therapy)

Beta radiation (typically using strontium-90) was applied postoperatively to inhibit fibroblast proliferation and reduce recurrence. This technique has several advantages including significantly reducing recurrence when used adjunctively and being effective in cases of aggressive or recurrent pterygium. However, there are disadvantages associated with beta radiation. It carries the potential for serious complications, such as scleral thinning, necrosis, delayed healing, and cataract formation. In addition, this technique requires access to specialized radiation equipment and adherence to safety precautions. Given these risks and lack of availability, the use of beta radiation is not routinely performed nor recommended.

Mitomycin C

Mitomycin C (MMC) is an antimetabolite commonly used intraoperatively (typically at a concentration of 0.02% for 1–2 minutes) to inhibit fibroblast activity and prevent recurrence. It is particularly advantageous as an adjunct treatment to reduce recurrence rates, especially in high-risk or recurrent cases. However, the use of MMC carries certain risks, including the potential for sight-threatening complications if not used properly, scleral melt, delayed epithelial healing, and secondary infections.[6] Therefore, MMC treatment requires careful dosing and technique.

MMC is widely used as an adjunct with both bare sclera and graft techniques, especially in recurrent pterygium surgery.[7] The bare sclera technique, where the pterygium is excised and the scleral bed is left uncovered, is a simple and quick procedure. When combined with MMC, it reduces recurrence rates compared to bare sclera alone. However, it remains inferior to techniques involving tissue grafting.

Conjunctival Autograft

After pterygium excision, a conjunctival graft (typically from the superior bulbar conjunctiva) is transplanted to cover the bare sclera. This technique is considered the gold standard for primary pterygium due to its numerous advantages.[8] It has low recurrence rates (2–15%), provides good cosmetic outcomes, and can be performed using either sutures or fibrin glue.

However, there are some disadvantages to this method. It is technically more demanding and takes longer to perform compared to the bare sclera technique. Additionally, in cases of bilateral or recurrent pterygium, the availability of conjunctiva may be limited. Despite these challenges, the conjunctival graft remains the most commonly used and preferred method for primary pterygium surgery.[9,10,11]

The following pearls can enhance surgical outcomes and reduce complications.

Preoperative Evaluation and Planning

A thorough preoperative assessment is vital. This evaluation should include an assessment of tear film stability, ocular surface inflammation, and the extent of corneal involvement. Corneal topography is an important preoperative tool in the evaluation and planning of pterygium surgery. It provides detailed information about the corneal curvature and surface irregularities that may not be evident on a slit-lamp exam alone.

The benefits of preoperative topography are numerous. Firstly, it allows for the assessment of corneal distortion. Pterygium can induce with-the-rule astigmatism, typically flattening the horizontal meridian. The larger and more advanced the pterygium, the more likely it is to cause irregular astigmatism and decreased visual acuity.

Secondly, topography helps determine surgical indication. Significant topographic distortion or steepening/flattening may indicate the need for surgery, even if the lesion is not visually encroaching on the visual axis.

Thirdly, it guides surgical planning by documenting the preoperative status, which is essential for assessing the visual and refractive impact of surgery postoperatively. It is also useful for identifying irregular astigmatism that may improve after surgery.

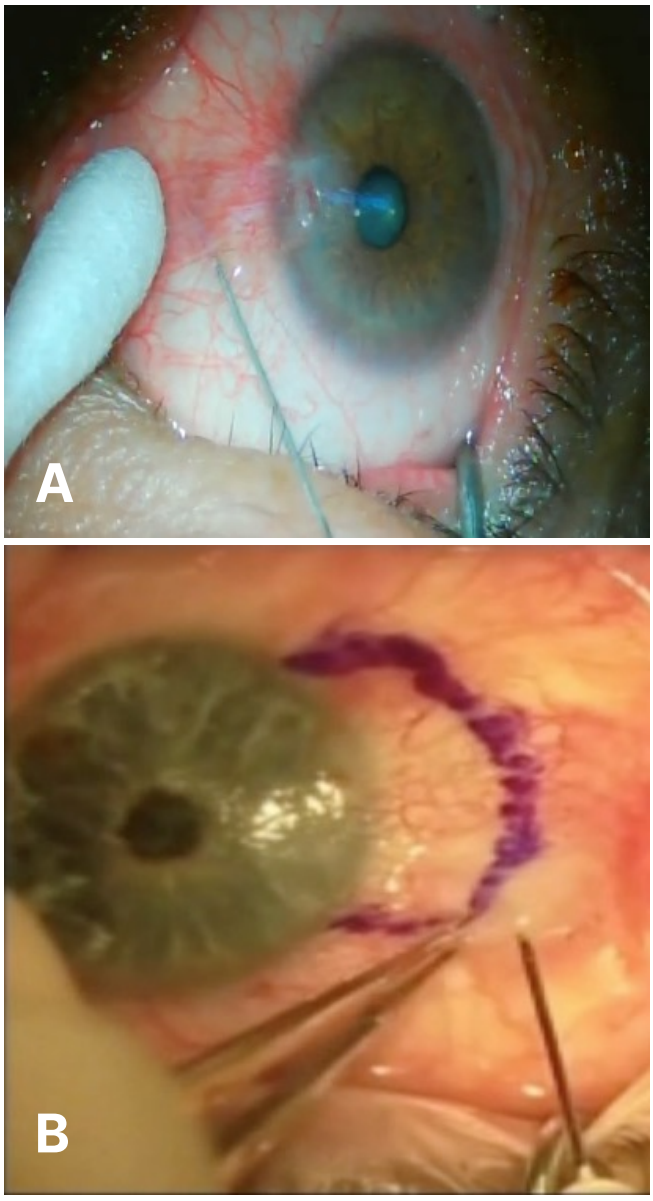

Figure 2. A: Subconjunctival anesthesia injection. **A.** 30G needle pinching under the pterygium. **B.** Injection placed after marking the area of excision; *courtesy of Randall Ulate, MD*

Lastly, topographic images are valuable for patient counselling. They can help explain the potential visual benefits to patients beyond just cosmetic improvements. This is particularly helpful for setting realistic expectations, especially in cases of longstanding or recurrent pterygium where some corneal distortion may be permanent.

Surgical Technique

Marking the Area to Excise

Proper preoperative marking of the area to be excised is crucial for achieving a complete removal, optimizing the graft size, and ensuring a clean surgical field.

It is important to identify the extent of the pterygium, which involves several steps. Begin by examining both the head (corneal extension) and the body (conjunctival portion) of the pterygium. Note the vascularized fibrovascular tissue, which can often extend deeper than it appears. Next, determine the limbal involvement and any associated Tenon's capsule thickening.

Using a Gentian violet marker, caliper, or surgical marking pen is recommended for precision. A corneal ruler or dot marking can help guide the dissection margins. When marking the conjunctival incision, place it 1.0-2.0 mm posterior to the limbus, around the body of the pterygium. Include a margin of normal-looking conjunctiva to ensure complete removal of fibrovascular tissue. Avoid excessive excision of healthy conjunctiva, especially in recurrent cases where the conjunctiva may be limited.

Anesthesia

Topical anesthesia with a supplemental subconjunctival injection ensures patient comfort. Careful administration minimizes chemosis and provides a clearer surgical field. Lidocaine plus epinephrine is recommended **(Figure 2)**.

Gentle and Complete Excision

Meticulous removal of the pterygium head and body is essential. Begin by dissecting the fibrovascular tissue cleanly off the cornea, preserving as much normal conjunctiva as possible. It is generally recommended to begin the excision on the conjunctival side, rather than directly at the cornea **(Figure 3)**. This approach allows for a more controlled dissection, better tissue plane identification, and more complete removal of the pathological tissue.

For the conjunctival incision, make an incision posterior to the body of the pterygium (~1-3 mm from the limbus). Elevate the conjunctiva to expose the underlying fibrovascular tissue and Tenon's capsule **(Figure 4)**.

When dissecting the fibrovascular tissue, carefully remove it en bloc, including the associated Tenon's capsule. Use blunt Westcott scissors to separate the tissue from the underlying

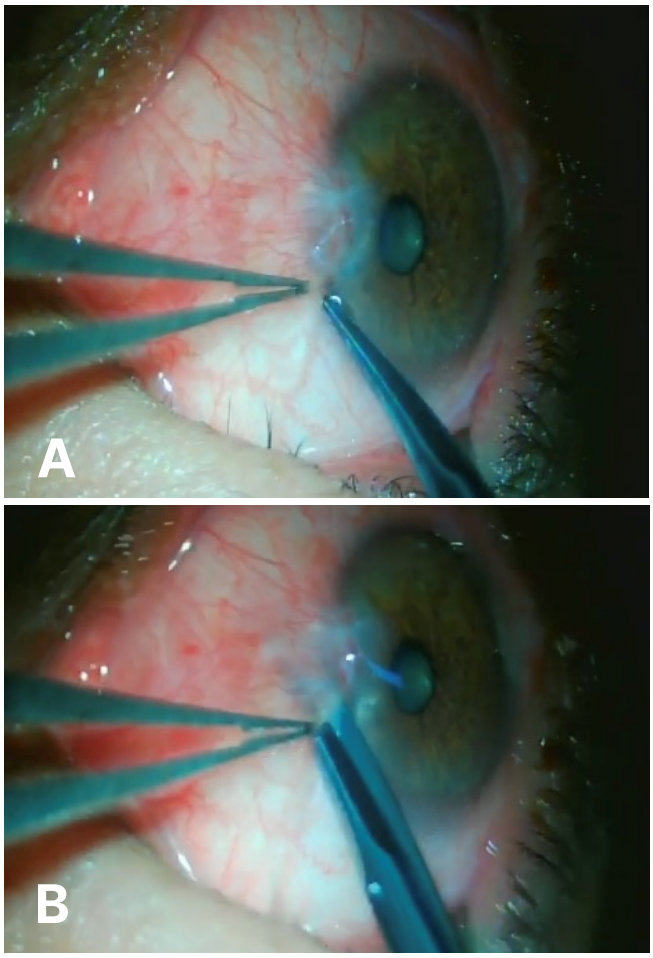

Figure 3. A. Conjunctival incision using Wescott scissors. **B.** Subconjunctival blunt dissection; *courtesy of Randall Ulate, MD*

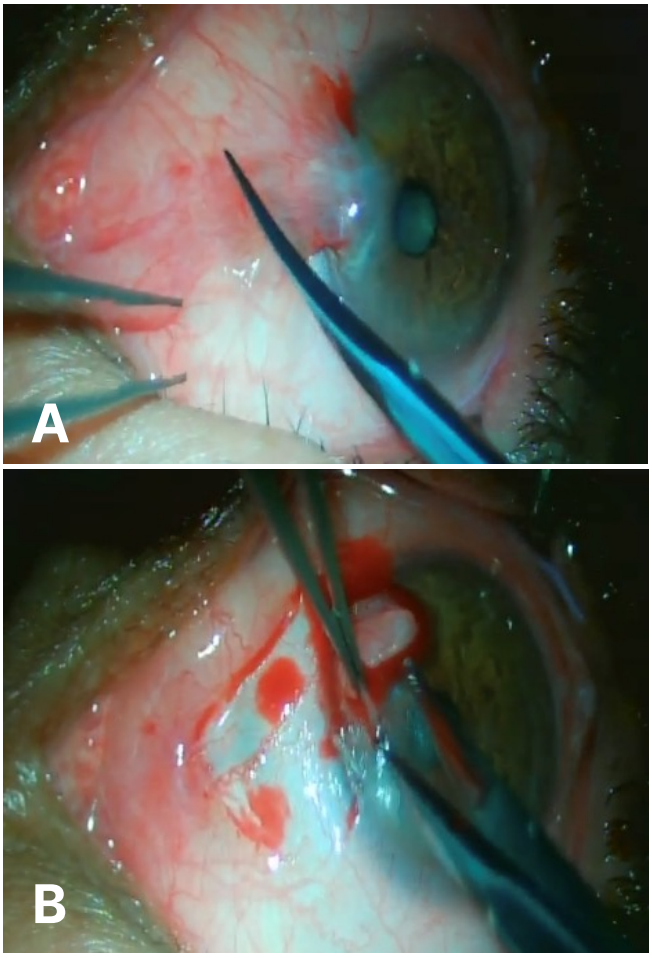

Figure 4. A. Conjunctiva is cut posterior to the body of pterygium. **B.** Pterygium separated from sclera; *courtesy of Randall Ulate, MD*

sclera. Ensure the dissection is in the correct plane (between Tenon's and sclera) to minimize bleeding and trauma.

Once the posterior dissection is complete, proceed anteriorly toward the limbus. At the limbus, sharply cut across the insertion of the fibrovascular tissue. After mobilizing the body, gently peel the pterygium head off the corneal surface. Use a crescent blade, 15 blade scalpel or Beaver blade to shave the remaining fibrous tissue off Bowman's layer. Smooth the corneal surface as needed with the blade or diamond burr (rarely necessary if the superficial keratectomy was made in the correct plane) **(Figure 5)**.

Why Start on the Conjunctival Side?

Starting on the conjunctival side results in better visualization and tissue handling. It also reduces the risk of buttonholing the conjunctiva, allows for complete removal of Tenon's tissue, reducing recurrence, and helps maintain anatomical planes and minimizes trauma.

Surgical Pearl

"If you remove only what you see, you'll leave behind what causes recurrence." That is why dissecting from the conjunctival side and ensuring Tenon's capsule is included is key to long-term success.

Scleral Bed Smoothing

After excision, the scleral bed should be smooth and free of Tenon's remnants. This can be achieved with light scraping with the same blade previously used for the superficial keratectomy. An uneven bed can lead to graft irregularities and poor healing. Avoid excessive cautery, as it may promote scarring and recurrence.

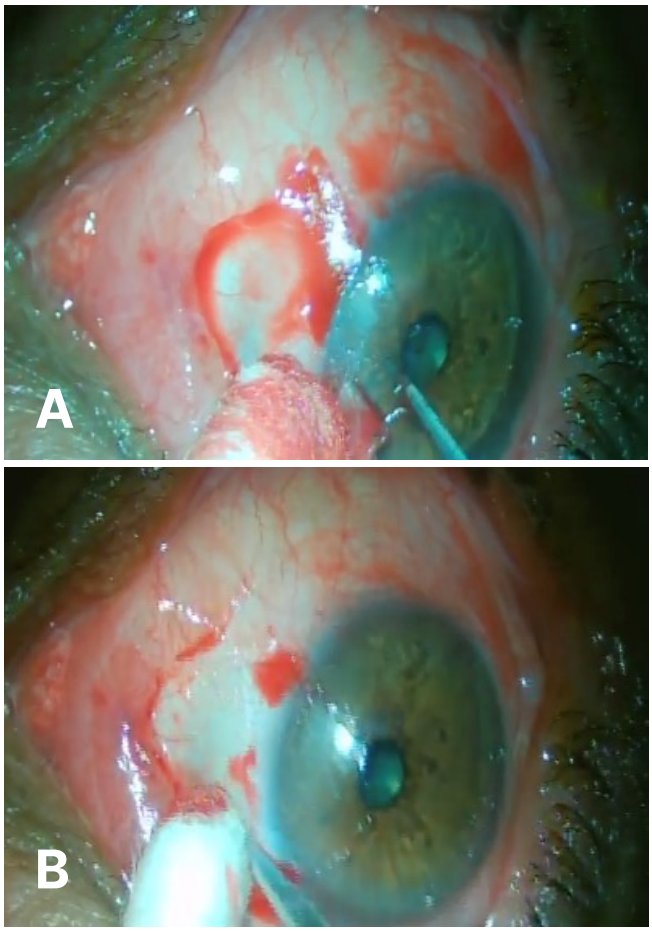

Figure 5. A. Superficial keratectomy. **B.** Smooth corneal and scleral surface; *courtesy of Randall Ulate, MD*

Conjunctival Autografting

A conjunctival autograft, preferably sourced from the superior bulbar conjunctiva, is widely regarded as the gold standard for reducing recurrence. Key techniques involve sizing the graft slightly larger than the bare scleral defect. This begins by measuring the defect size after excising the pterygium and exposing the bare sclera **(Figure 6)**. Subsequently, mark the donor graft to match or slightly exceed the size of the excised area **(Figure 7)**.

If using fibrin glue, slightly oversize the graft for better edge apposition. In recurrent pterygium removal surgery, a graft containing some limbal stem cells can reduce recurrence rates. However, for primary pterygium surgery, a conjunctival autograft without stem cells will suffice and surgical trauma to the superior limbus can be avoided. Include minimal Tenon's tissue to prevent bulkiness. Ensure the graft is oriented correctly (epithelium side up).

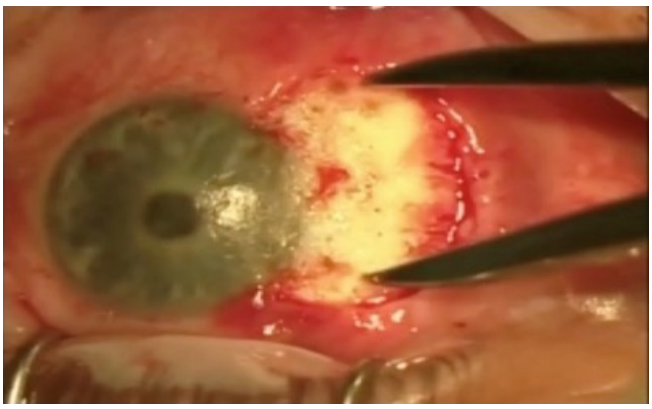

Figure 6. Measurement of bare sclera; *courtesy of Randall Ulate, MD*

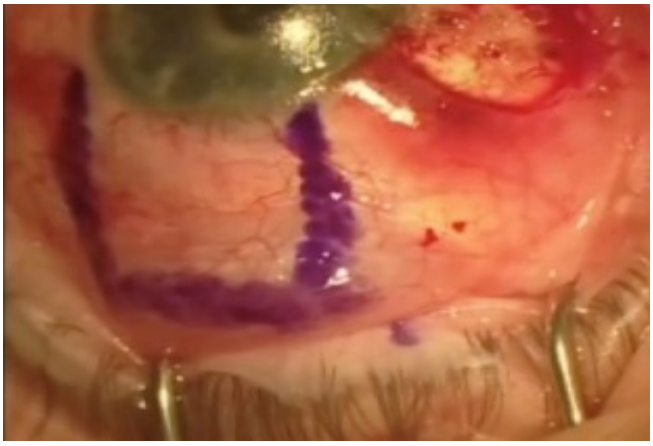

Figure 7. Marking conjunctival graft; *courtesy of Randall Ulate, MD*

You can secure the graft with fibrin glue or sutures. Fibrin glue offers shorter surgery time and better patient comfort, while sutures may be preferred in certain settings. Conjunctival grafts secured with fibrin glue during pterygium surgery are as stable as those secured with sutures and produce significantly less inflammation. Tissue adhesives have revolutionized conjunctival autograft fixation in pterygium surgery by offering faster, sutureless techniques with excellent cosmetic and functional outcomes **(Figure 8)**.[12]

Fixation of the Graft with Fibrin Glue

First, prepare the bed, ensuring that the scleral bed is clean and dry. Achieve meticulous hemostasis (any bleeding can prevent adhesion). Apply small drops of fibrin glue.

Next, gently position the conjunctival autograft over the glued area. Carefully align the limbal edge with the limbus **(Figure 9)**. Using a forceps, gently press the edges of the graft against the host conjunctiva for 1–2 minutes to

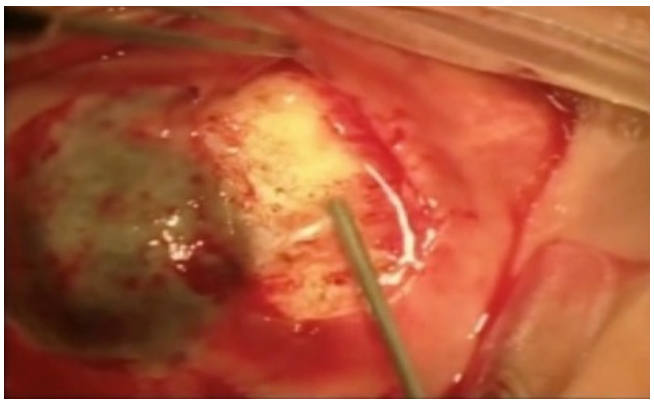

Figure 8. Fibrin glue is placed on the bare sclera previous to position the conjunctival graft; *courtesy of Randall Ulate, MD*

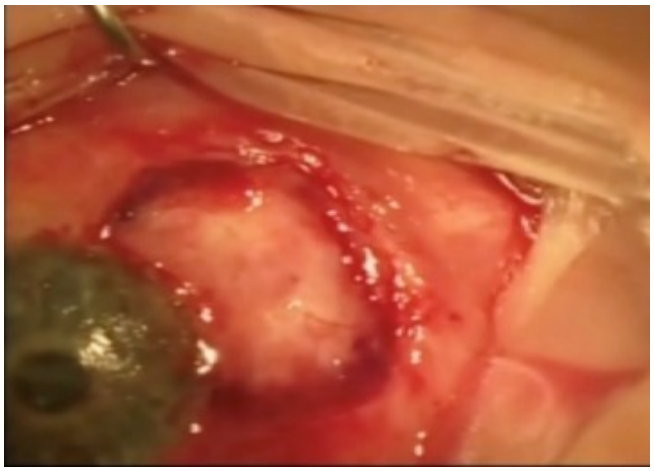

Figure 9. Conjunctival graft holding in position; *courtesy of Randall Ulate, MD*

ensure adhesion. Allow time for polymerization, as fibrin glue typically sets in 10–60 seconds, depending on the brand used.[13] Once the graft is in place, avoid manipulating it after placement.

Fixating the Conjunctival Autograft with Sutures in Pterygium Surgery

Although tissue glue is gaining popularity, suture fixation remains a widely used and effective method for securing conjunctival autografts, especially in settings where glue is unavailable. A commonly used suture material for conjunctival graft fixation is 10-0 Nylon, which is favoured for its tensile strength, low tissue reactivity, and fine calibre that minimizes tissue trauma. While alternative options such as 9-0 or 10-0 vicryl are available, nylon is preferred when longer graft stability and minimal inflammation are desired.

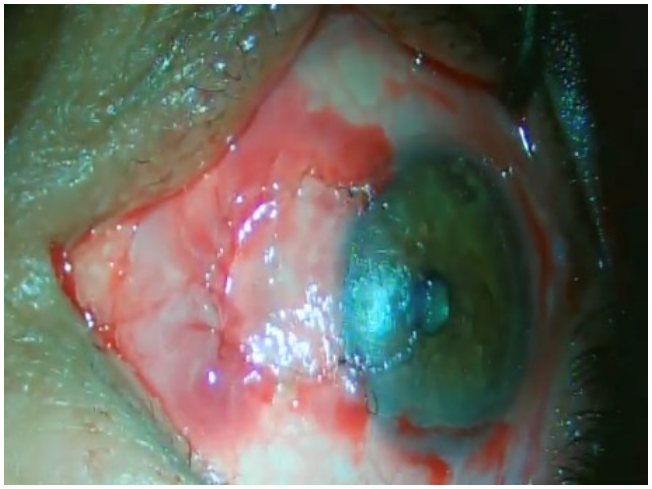

Figure 10. Conjunctival autograft fixated with 10-0 Nylon suture; *courtesy of Randall Ulate, MD*

Suturing Techniques

For interrupted sutures, place four to six interrupted 10-0 nylon sutures at the edges and corners of the graft. This technique ensures edge-to-edge apposition without causing tension or redundancy.

Running (continuous) sutures, while faster, are slightly more technically demanding. They are typically used for the limbal edge or to anchor one side of the graft. However, there is a risk of cheese-wiring if the sutures are placed under tension.

A combination technique can be used, where interrupted sutures are placed at the corners, and a running suture is used along the limbal edge. Additionally, optional limbal anchoring can be employed. Placing a suture at the limbus helps maintain orientation and ensure an anatomical match (especially if a limbal stem cell barrier is being restored) **(Figure 10)**.

Minimize Recurrence with Adjunctive Therapies

MMC at a 0.02% concentration applied intraoperatively under the rim of retracted conjunctiva for 1–2 minutes has shown efficacy in reducing recurrence, especially in cases of aggressive or recurrent pterygium.[14,15] However, care must be taken to avoid complications such as scleral thinning. We recommend using MMC for recurrent pterygium, and only rarely for primary cases.

Postoperative Care

Post-surgical care includes several steps. Patients are usually prescribed topical antibiotics and corticosteroids which are tapered over a period of 4–6 weeks. Lubricants are recommended to support ocular surface healing. Wearing sunglasses is recommended to protect the eyes from UV light. Close follow-up during the early weeks is necessary to monitor for graft displacement, infection, or recurrence signs.

Complications

Common complications following surgery include graft edema, graft displacement or loss, Dellen formation, infection, pyogenic granuloma, recurrence, symblepharon, scleral thinning or necrosis. However, most of these are preventable with careful surgical technique and early intervention.

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Financial Disclosures

R.U.: None declared.

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