

Contemporary Management of Pseudo-exfoliation Glaucoma and Treatment Options

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Abstract

Pseudo-exfoliation glaucoma (PXFG) is the most common *secondary* open angle glaucoma. Accumulation of exfoliative debris in the angle and subsequent IOP elevation are thought to help make PXFG more recalcitrant to topical therapy than primary open angle glaucoma. This review discusses laser therapy treatment in the form of selective laser trabeculoplasty for open angle PXFG, as well as the risk of an angle closure component in PXFG eyes and several possible underlying mechanisms. This is followed by a literature-based discussion on the risks and benefits of laser peripheral iridotomy or cataract surgery to open the angle. The literature on the many available options for microinvasive glaucoma surgery (MIGS) for PXFG is also reviewed. This review provides an overview of MIGS subtypes and summarizes study data on several of the better-studied options for PXFG. Lastly, the efficacy and risks of filtering procedures including trabeculectomy and tube shunts for PXFG are examined.

KEY WORDS:

Pseudo-exfoliation, glaucoma, selective laser trabeculoplasty, angle closure, microinvasive glaucoma surgery, trabeculectomy

INTRODUCTION

Pseudo-exfoliation syndrome (PXF) is an age-related systemic microfibrilopathy. Several genes have been linked to pseudo-exfoliation (PXF), most commonly LOXLL1, which is a member of a family of lysyl-oxidase enzymes.¹ These enzymes play important roles in the creation of elastic fiber. Dysregulated production of elastin fibers is thought to result in the formation of elastotic exfoliation material throughout the body.² PXF has traditionally been linked to Scandinavia, due to its high incidence there. For example, among 66-year-olds in a northern Sweden municipality, roughly one in four had PXF, and women were twice as likely to be affected as men.³ More recent epidemiological studies have confirmed an increased risk of PXF with residence further from the equator. More specifically, exposure to colder ambient temperatures and surfaces such as snow and water, which provide increased solar reflectivity, has been linked to the risk of PXF worldwide, and not just in those of Scandinavian descent. Those with an urban lifestyle and who wear sunglasses more often may have a lower risk of pseudo-exfoliative glaucoma (PXFG). Ultraviolet radiation may trigger gene expression linked to the formation of exfoliative material, while lower external temperatures may increase precipitation of exfoliative material out of the aqueous.⁴

PXFG is often described as the most common identifiable (i.e., secondary) cause of *open-angle* glaucoma; and commonly goes undiagnosed until it is quite advanced. Compared to primary open angle glaucoma (POAG), PXFG eyes often have a higher peak intraocular pressure (IOP), more IOP fluctuations, quicker field deterioration, elevated rates of failure of topical medication and more frequent need for glaucoma surgery. This aggressive nature of PXFG contributes to significantly higher rates of office visits, cataract surgery, glaucoma surgery and overall eyecare costs compared to POAG.⁵

Patients with PXFG often require maximal medical therapy (MMT); frequently, however, this is still not enough to adequately slow progression.⁶

The most commonly described mechanism for the development of PXFG involves IOP elevation due to exfoliative and pigment deposits in the trabecular meshwork (TM) impairing aqueous drainage. In phakic eyes in particular, there is a closer posterior iris and anterior lens capsule proximity. Pupillary movement causes the iris to scrape exfoliative material from the anterior capsule, liberating it. The PXF material on the lens capsule likely also contributes to the rupture of posterior iris epithelial cells, liberating pigment.⁷ The *involved* eye in clinically unilateral PXFG shows a higher IOP and diurnal variation than the fellow eye. This is likely due to increased aqueous drainage resistance through the TM in PXF.⁸ Using a triggerfish contact lens sensor, Tojo showed that the 24-hour range of IOP fluctuations in eyes with PXF was significantly larger than that in controls.⁹ Konstas showed that the IOP was more than 15mmHg in 35% of newly diagnosed/untreated PXFG eyes, compared to only 7.5% of eyes with POAG. The mean *range* of IOP fluctuation in eyes with PXFG was 13.5 mmHg, which is significantly greater than the 8.5 mmHg range observed in POAG. These fluctuations may explain the poorer response to medical therapy and more aggressive field and optic nerve progression in PXFG.¹⁰ Koz proposed IOP fluctuations as a main driver of PXFG with ‘normal’ eye pressures in the office.¹¹

MEDICAL (TOPICAL) MANAGEMENT OF PXFG

Due to the higher IOP fluctuation and more aggressive nature of field loss in PXFG, close follow-up may be prudent. A lower target IOP (relative to a POAG patient with the same maximum IOP and current level of field loss) may be considered.¹² Although not always realistic or feasible, it has been recommended that clinicians take at least 2-3 IOP measurements (at different times of day) to have the best chance at observing the maximal IOP value with which a target IOP can be calculated.¹³

Prostaglandin analogs are typically the first topical IOP-lowering agents that patients with open-angle PXFG are started on, at once-daily dosing.⁶ Prostaglandin analogs appear to give a 30-35% IOP reduction in open angle PXFG eyes and decrease IOP by increasing outflow through the uveoscleral outflow pathway. In PXFG, latanoprost 0.005% has been shown to give a better diurnal range of IOP control than twice-daily timolol 0.5%.¹⁴ Travoprost 0.004% and bimatoprost 0.03% have been shown to give slightly significantly better IOP control than latanoprost.^{15,16} Despite the typically good response to these analogs, *combined* medical therapy is often necessary in PXFG eyes, due to aggressive progression rates as well as the fact that many eyes are already quite advanced when diagnosed.¹⁷

In patients with PXFG who can not tolerate or respond to prostaglandins, the addition of twice-daily dorzolamide 2% to a dosing regimen already consisting of timolol 0.5% further markedly lowered IOP at all time points while reducing the diurnal IOP range.¹⁸ A twice-daily combination of brinzolamide 1%-brimonidine 0.2% lowered IOP by an additional 19% (4.02±3.17 mmHg) in 35 patients with PXFG who were already receiving a once-daily prostaglandin *with or without* timolol 0.5%.¹⁸ Rho-kinase inhibitors, namely netarsadil, decrease TM outflow resistance. Netarsadil has been shown to exert a significant IOP-lowering effect, even in POAG patients using 3 or more glaucoma medications.¹⁹ Netarsadil has not yet been extensively studied in PXFG patients, but a small retrospective study of non-severe PXF OHTN or PXFG patients who were already receiving at least one medication showed statistically and clinically significant reductions in mean IOP relative to baseline (mean baseline IOP 25± 2.4 mm Hg; final mean IOP of 21.3± 5.3 mm Hg at week 25) on this agent.⁷ Studies specifically targeting PXFG are needed on the performance of latanoprostenebunod, a new well-performing IOP-lowering agent that is broken into latanoprost acid and nitrating, donating butanediol mononitrate. Since exfoliative material increases resistance to outflow through the TM and nitric oxide promotes TM relaxation and subsequently increased outflow facility, it may theoretically work well in PXFG.²⁰

Pilocarpine was commonly used in the past for PXFG but may contribute to posterior synechiae formation and/or exacerbate preexisting anterior subluxation secondary to zonulopathy. This in turn may increase the risk of pupillary block angle closure.⁶ However, Angelilli and Ritch argue that pilocarpine 2% at a reduced dosing frequency can blunt early-morning IOP spikes in PXFG eyes while opening the angle more and increasing outflow through the corneoscleral pathway.²¹ Once maximally tolerated medical therapy fails to control IOP and progression, it is imperative to proceed to a laser or surgical approach in open-angle PXFG, as in POAG, in an attempt to further lower IOP and IOP fluctuations.⁶

LASER MANAGEMENT OF PXFG

Selective laser trabeculoplasty (SLT)

SLT uses a doubled pulsed-frequency of a neodymium (Nd):YAG laser to selectively target melanin in the trabecu-

lar meshwork. It is thought to exert an IOP-lowering effect through stimulation of phagocytic cell activity in the TM to clean up 'clogging debris'.²² Over a 1-year follow-up period, Goldenfeld showed that 180° SLT lowered mean IOP from 26.01mmHg \pm 2.5 to 17.8mmHg \pm 2.8 mmHg (31.5% reduction); and decreased the mean number of topical medications from 2.8 to 2.3 at 12 months in 57 PXFG eyes that had been previously uncontrolled on maximal medical therapy.²³ There do not appear to be as many published studies on SLT as a primary therapy in PXFG, even though it seems reasonable to consider this option in patients who are expected to have poor compliance with topical treatment. Shazly studied 180° SLT as a primary therapy in 18 PXFG eyes with a mean pre-operative IOP of 25 mmHg; 74% of the eyes achieved a decrease in IOP of at least 3mmHg at 1 year while not requiring subsequent intervention when observed for an average of 20 months.²⁴ Even when successful, the IOP-lowering effect of SLT diminishes after a few years, but the procedure is repeatable even in previously lasered angle portions.²⁵ After the iStent and trabectome MIGs procedures discussed below, SLT can be performed when needed with expectations guarded for IOP-lowering and communication to the patient that there is a likelihood of an eventual need for a filtering procedure.^{26,27}

Some publications have used 360° SLT treatments in one sitting for PXFG.²⁸⁻³⁰ However, 360° SLT may not be prudent because of the relatively higher degree of angle pigmentation in PXF eyes. As a result, PXF eyes suffer higher energy absorption and resulting inflammation for a given laser energy setting.³¹ PXF eyes themselves are also predisposed to more inflammation after procedures in general, not just SLT. Bettis documented a case series of 5 PXFG patients post SLT who had persistent IOP spikes with associated corneal edema. The three highest spikes were 17, 18 and 24 mmHg higher than the pre-SLT IOP. All eyes required subsequent trabeculectomies. 3 were recommended to receive corneal transplants.³² When 180° SLT is performed, the other 180° can be completed later, if needed, after assessing the effect of treatment at 6-12 weeks from the original treatment.^{24,33} To lower the risk of complications such as transient post-operative IOP spikes in PXF eyes, it is also prudent to use the lowest possible energy setting. This can be 0.1mJ lower than the energy that on average forms cavitation bubbles, where more highly pigmented TMs require less energy.³¹ IOP spikes post-SLT in high-risk patients such as PXF tend to take place within 24 hours. Thus, it may be prudent to perform the procedure in the morning, and then check at 45-60 minutes post-procedure and once more in the afternoon, as is done by some surgeons performing cataract surgery on high-risk eyes.³³ An alpha-2 agonist such as brimonidine 0.2% or 0.5% apraclonidine may be instilled before and after the procedure to quell a potential IOP spike.³²

SLT is contraindicated in angles where TM cannot be safely visualized.³⁴ Moreover, SLT can lead to PAS formation itself; though the global incidence is roughly estimated to be 0-3% of patients.³⁵ An anterior chamber (AC) depth lower than 2.57 mm has been shown to predict a low effectiveness of SLT.³⁶ Further, a shallower AC is associated with a higher post-SLT risk of corneal endothelium damage.³⁷ Pertinently, PXF itself can predispose to corneal endotheliopathy.³⁸ Ornek and Ornek found a statistically significant fall in density and an increase in the coefficient of variation of endothelial cells 1 week after SLT in PXF patients; though this effect reversed at 1 month. Further studies are needed to confirm that this effect is only transient.³⁹

Laser Peripheral Iridotomy (LPI)

Angle closure that obstructs aqueous outflow, causing elevated IOP, has been found to be more common in PXF eyes than in non-PXF eyes.⁴⁰⁻⁴² Overall, eyes with exfoliation syndrome may be more prone to chronic angle closure, which tends to be less symptomatic than acute angle closure.⁴⁰ The risk of angle closure in PXF may not be as axial length-dependent as in primary angle closure.^{41,42} The iris in PXF is more rigid due to PXF material infiltration and atrophy/fibrosis of the iris. The PXF iris is therefore relatively flatter and less convex than irises in primary angle closure glaucoma (PACG).⁴⁰ The pressure induced by continuous aqueous production in the posterior chamber may induce the rigid iris to bulge anteriorly at its thinnest/weakest point, the root.⁴³ This in turn may create a localized narrowing of the angle, resembling a plateau configuration on gonioscopy. Evidence that PXF eyes do not have a *true* plateau iris syndrome (PIS) comes from LPI successfully widening the angle in cases of PXF angle closure.⁴⁰ LPI may open the angle because the cause of narrowing is not an anteriorly rotated ciliary body, as in PIS, but rather relative pupillary block.^{40, 44,45} The iris-lens contact distance has been found to be greater in PXF eyes, likely increasing the risk of pupillary block.⁷ This contact also likely enhances friction between both structures, increasing inflammation and iris pigment epithelial cell rupture.⁷ This inflammation as well as the 'sticky' PXF material may increase the predisposition toward posterior synechiae formation, further increasing the risk of pupillary block.⁴⁰ PXF patients tend to develop cataracts at an early age and may present with denser cataracts.^{46,47} Therefore, another possible explanation for why PXF eyes are more prone to angle narrowing is that increases in lens thickness in PXF eyes worsen pupillary block and/or predispose towards angle closure.⁴² A final theory is that zonular weakness

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in PXF eyes leads to anterior subluxation, which in turn reduces AC depth and angle width.⁴⁸ Any eye with PXF and asymmetric anterior depth may be suspected for zonulopathy.⁴⁹ Phacodonesis or iridodonesis are clinically observable signs of reduced zonular function. However, it is important to note that zonular weakness is actually more commonly identified intra-operatively, namely during cataract surgery.⁵⁰ Identifying occludable angles in eyes with PXFG is important given the particularly poor response these eyes will have to medical therapy alone; instead, iridotomy or cataract surgery should be considered.^{1,6}

The LPI procedure 'is generally considered safe' provided non-excessive energy is used, the cornea is not edematous, and the AC is not excessively shallow or inflamed.⁵¹ However, it should be at least acknowledged that there is a reported risk of LPI-induced zonule damage.⁵²⁻⁵⁴ This is potentially relevant in a PXF eye, which is already predisposed toward zonulopathy.⁴⁹ Reassuringly, in a retrospective review of 40 eyes with zonulopathy noted intra-operatively during cataract surgery, LPI was actually shown to *not* be associated with an increased risk of zonulopathy. However, this study involved PACG and not PXF eyes, which are already predisposed to zonulopathy.⁵⁵ Further evidence/study in PXF eyes is needed. Another potential argument against proceeding with LPI prior to cataract surgery includes the risk that LPI itself may damage the corneal endothelium or Descemet's membrane in a patient with shallow anterior chambers;^{56,57} and PXF eyes are also already predisposed towards endotheliopathy.³⁸

Synechiolysis in cases of chronic angle closure can be combined with cataract surgery and completed with surgical instruments such as a cyclodialysis or Mori gonio spatula pressing against peripheral edges of the anterior iris next to points of PAS.⁵⁸ Some surgeons favor the injection of high-molecular-weight viscoelastics (visco-synechiolysis) near the angle to resolve PAS, while avoiding surgical trauma to the angle and iris.⁵⁹ We were not able to find any studies in which synechiolysis was used on PXF eyes with synechia in particular.

Cataract Surgery for PXFG

It has been established that cataract surgery lowers IOP by an average of 1-3 mmHg in healthy or POAG eyes, with around 80% of patients maintaining this reduction at 5 years.⁶⁰ IOP may on average actually drop a little more in PXF eyes post cataract surgery.⁶¹⁻⁶⁴ A meta-analysis showed an IOP drop of -5.8mmHg (95% CI: -9.5 to -2.0) in PXFG eyes versus -2.7mmHg (95% CI -3.7 to -1.7) in POAG eyes following cataract surgery.⁶⁴ Another meta-analysis showed that among 5 PXFG studies with a mean follow-up time of 34 months, IOP decreased from a mean before surgery of 20.7 mmHg with 1.7 medications to 16.6 mmHg with 1 medication.⁶⁵ These patients had IOP that was medically controlled prior to cataract surgery and the authors concluded this was a moderate IOP reduction relative to those with PACG who

had a 'marked' reduction and those with POAG who had a 'mild' reduction.⁶⁶ Cataract surgery has also been shown to possibly slow ganglion cell progression.⁶³ Thorough irrigation of the anterior chamber and angle after IOL implantation might also contribute to this significant decrease in IOP in PXF/PXFG eyes by removing exfoliative debris, thereby decreasing TM outflow resistance.⁶³

IOP in PXF eyes may also benefit from increased TM access via a wider AC angle. Cataract surgery has been shown to significantly increase angle width as well as other markers - AC depth and volume. In fact, this widening and increase in volume appears to be greater in PXF/PXFG eyes versus non-PXF eyes.⁶⁷ There is also more space created between the posterior iris and the anterior IOL. This causes an expected reduction in iris-lenticular chaffing and in turn reduced liberation/release of pigment and exfoliative material that can reduce TM outflow.⁶⁸ One of the sources of exfoliative material, the anterior lens capsule, is also partially removed during cataract surgery.⁶⁸ Rao reported that 33 PXFG eyes with occludable angles demonstrated a statistically significant reduction in IOP fluctuation as measured by max-min IOP difference along the diurnal curve post cataract removal.⁶⁹ Given the above, glaucoma surgeons appear to be open to the practicability of (early) cataract surgery in PXFG patients with mild lens opacity.⁷⁰

Traditional arguments for delaying cataract surgery include greater postoperative inflammation and higher risk of postoperative IOP elevation in PXF.⁶⁷¹ PXF patients often need a more intensive and longer postoperative course of steroid.⁶ Characteristics such as zonular laxity/weakness, poor pupil dilation, posterior synechiae, and shallower than average AC increase the risks of cataract surgery complications in PXF eyes. These risks/complications include but are not limited to delayed IOL decentration, capsular rupture, postoperative pseudophakodonesis, anterior capsule contraction, corneal endotheliopathy, choroidal hemorrhage, and vitreous loss/ anterior prolapse.^{71,72} A monofocal rather than toric or multifocal IOL may be considered in PXF due to a risk of delayed IOL decentration in the capsular bag as a result of progressive zonulopathy.⁷³ Gauging of current and projected contrast sensitivity levels, which will decrease as glaucoma progresses, is important when counselling a PXFG patient on whether multifocal IOL is recommended.⁷⁴

The risk of complications in cataract surgery with PXE can be lessened with surgical experience, technique modifications such as the soft shell viscoelastic technique and a wider capsulorhexis, and adjunctive devices such as a capsular tension ring.^{49,75} With refined technique and preparation, Shingleton showed no differences in the risk of cataract surgery complications in 100 eyes with unilateral PXF versus the fellow eyes.⁴⁹ Furthermore, it may actually be beneficial to proceed to cataract surgery earlier in PXF to avoid an increased risk for complications with more progressively advanced zonulopathy, impaired pupillary dilation and cataract density.^{49,76} End-stage PXFG is also associated with a high risk of considerable post-operative IOP elevation even if IOP is relatively controlled pre-operatively and cataract surgery is uncomplicated.⁷⁷

Cataract surgery in PXFG can be combined with trabecular aspiration or significantly more irrigation of the AC and angle than is used for healthy eyes. Trabecular aspiration after IOL implantation vacuums exfoliative debris out the TM via an irrigation-aspiration probe, supposedly unblocking filtering pores. Aspiration has been shown to possibly reduce IOP and decrease the need for glaucoma medications more than cataract surgery alone in the short term;^{78,79} but there have not been enough studies with an adequate sample size. The effect of aspiration may dwindle after 2 to 3 years with the accumulation of progressively more exfoliative material in the TM/angle.⁸⁰ Recently, Tran reported an approach with a new pressurized washout technique for PXF material in the AC angle/TM, which significantly decreased IOP and the number of topical medications required post-surgery.^{81,82} More studies with a larger sample size and a prospective design, and from different authors, will be needed.

Microinvasive Glaucoma Surgery for PXFG

Microinvasive Glaucoma Surgery (MIGS) is advertised to have fewer severe complications, less risk, shorter surgical time, and more rapid recovery than trabeculectomy and glaucoma drainage devices (GDD).⁸³ The IOP-lowering effect of MIGS is weaker than that of trabeculectomy. MIGS was intended to fill the gap in treatment options between medical therapy and more aggressive traditional surgery options.⁸⁴ MIGS may also decrease the number of topical medications needed long term to lessen dry eye symptoms and reduce the risk of non-compliance.⁸⁵

More well-powered randomized controlled trials (RCT) and other prospective studies are needed before we can recommend the use of one MIG over another in PXFG, since many options are now available. MIGs can be subdivided according to whether an ab externo or interno approach is used as well as by the tissue they target. Most studies involving PXFG eyes are on MIGS devices that bypass the TM, those that cut the TM, and those that drain

directly into the subconjunctival space. The first two, or *TM MIGS*, are not ideal in cases of advanced glaucoma where the opportunity cost of not obtaining maximum IOP control with the first procedure is high. However, less urgent/advanced cases spare the conjunctiva, maintain the option of subsequent filtration surgery, and require only one corneal incision (although gonioscopy-assisted transluminal trabeculectomy can require two incisions).⁸⁶

TM bypass MIGS devices include the iStent, iStent inject, iStent Infinite (all Glaukos Corp., Aliso Viejo, CA) and the Hydrus Microstent (Alcon, Geneva, Switzerland).⁸⁶ The newer iStent Infinite involves the injection of 3 stents and can be performed as a stand-alone procedure, whereas the others including the 2-stent involving *iStent inject* are indicated to be performed *during* cataract surgery.⁸⁷ iStent devices (Glaukos) are implanted ab interno and connect the AC and Schlemm's canal, bypassing the TM, and ultimately giving aqueous humor easier access to the scleral plexi and episcleral veins of the conventional outflow pathway.⁸⁶ Hengerer prospectively showed a mean 32% reduction in IOP and 64% fewer medications at 12 months after the injection of two second-generation iStent (injects) combined with cataract surgery in a subgroup of 15 PXFG eyes in various stages.⁸⁵ Ferguson showed that the implantation of 1 stent combined with cataract surgery offered a mean 27% reduction in IOP and a 50% mean reduction in IOP-lowering medications at 6 months in 115 PXFG eyes at various stages. Mean reductions in IOP and medication use of 4.71/0.9; 5.23/0.5; and 9.54/0.67 were shown in patients with mild (n=49); moderate (n=54) and severe (n=12) PXFG, respectively.⁸⁸ While both of the studies described above are very promising, both authors disclosed financial ties to Glaukos, the former was very small and the later was retrospective with a possible selection bias.^{85,87} In Ferguson's study, 7 PXFG eyes (6%) had an IOP spike ≥ 15 mmHg at any point during the 24-month follow-up period after the procedure, with most occurring in the first post-operative week.⁸⁸ iStent is discouraged in eyes with ongoing occludable/narrow angles, since the stent may occlude with the iris. Furthermore, in eyes with past chronic angle closure, the TM outflow system may have longstanding and irreversible damage.⁸⁶

MIGS studied in patients with PXFG that *remove* (rather than stent) the TM include the trabectome, Kahook Dual Blade (New World Medical, Cucamonga, CA) and gonioscopy-assisted transluminal trabeculectomy.⁸⁶ Trabectome or ab interno trabeculectomy provides high-frequency micro-electrocautery to about 3-4 clock hours of TM and Schlemm's canal along with simultaneous, continuous irrigation to remove exfoliative debris.⁸⁹ In a non-randomized prospective design study, Ting examined the effect of cataract surgery combined with a trabectome in 45 PXFG eyes with a mean preoperative IOP of 21.7 ± 8.4 . At 1 year, the mean decrease in IOP was -7.2 ± 7.7 mmHg, and 6.7% required a secondary procedure.⁹⁰ Ordan also prospectively studied the effects of a trabectome in 173 PXFG eyes, 40% of which had the procedure combined with cataract surgery. After a mean follow-up of 200 ± 278 days, IOP in the 173 eyes was on average reduced from 25 ± 5.9 mmHg to 18 ± 8.2 mmHg, and the number of medications was reduced from 2.0 ± 1.2 to 1.1 ± 1.1 .⁹¹ Importantly, a significant IOP-lowering effect has been seen in PXFG eyes that were only treated by trabectome itself, providing reassurance that cataract surgery is not the only source of an IOP-lowering benefit. Ting's trabectome-only PXFG group of 67 eyes had a pre-operative mean IOP of 29.0 mm Hg ± 7.5 (SD), and showed an average decrease in IOP of -12.3 ± 8.0 mm Hg at 1 year with a secondary procedure rate of 20%.⁹⁰ One longer-term but small-sized study found that 28 PXFG patients who were receiving treatment with trabectome-alone had a mean IOP reduction of 26% (23.1 ± 5.1 mmHg to 17.2 ± 6.1 mmHg) and a 29% (2.4 ± 1.0 to 1.7 ± 1.3) reduction in the number of topical medications after a median follow-up of roughly 3.5 years.⁸⁹ Nonetheless, both Jordan and Okeke found that trabectome-cataract surgery versus trabectome-alone was associated with less chance of failure, possibly due to the beneficial effects of increased angle width.^{91,92} According to Okeke, a trabectome can actually be used *off-label* in advanced PXFG eyes due to its low side-effect profile and efficiency, particularly when combined with cataract surgery.⁹² Although trabectome surgery is actually commonly performed before cataract surgery,⁹² it can also be performed after IOL implantation opens the angle for better TM access in narrow-angle patients without significant synechiae.⁹³⁻⁹⁴

Ting reported that 4/45 or 9% of PXFG patients had an IOP spike of 10 mmHg after combined trabectome and cataract surgery.⁹⁰ Hyphema, caused by reflux of blood from the collector channels, occurs in almost all cases of trabectome surgery, including in PXFG eyes, but usually resolves without additional surgical intervention. PAS may form in up to 14% of patients, and is more likely in younger patients. Multiple studies have shown better IOP-lowering and long-term survival responses to trabectome surgery in PXFG (vs POAG) and this has been postulated to be due to the removal of exfoliative debris.⁸⁹⁻⁹⁰

Kahook Dual Blade (KDB, New World Medical) excises a 3-4 clock hour strip of TM and the wall of Schlemm's canal.⁸⁶ KDB only requires a single corneal incision and removes TM in a more complete fashion than a traditional goniotomy knife, leaving significantly less residual TM and causing less collateral damage. One retrospective



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study without any disclosed financial connection to New World Medical involved 38 PXFG eyes with a mean pre-operative baseline IOP of 22.4 ± 7.4 mmHg on 2.7 ± 1.5 post-operative medications.⁹⁵ Thirty-six months after KDB combined with cataract surgery, IOP was significantly lower at 13.4 ± 2.3 mmHg on 2.1 ± 1.4 medications. This study also featured a POAG group of 110 eyes. This group at 9% had significantly fewer IOP spikes of >10 mmHg and fewer subsequent surgeries than the PXFG group (24%); though the PXFG group did have a greater proportion of patients with pre-existing severe-stage glaucoma. Hyphema occurred in 14.2% of cases *overall*, but cleared spontaneously without intervention in all cases. Other small sample-sized retrospective studies (with authors who disclosed relationships with New World Medical) have shown successful IOP-lowering in PXFG with KDB alone.⁹⁶⁻⁹⁷ The IOP-lowering effect may still be better when KDB is combined with cataract surgery though more long-term, prospective studies on KDB in PXFG are welcome.⁹⁶

Gonioscopy-assisted transluminal trabeculotomy (GATT) involves the ab interno attempted passing of either an illuminated catheter or thermally blunted 5-0 or 6-0 suture 360 degrees circumferentially within Schlemm's canal. Its proximal end is then pulled to externalize the catheter/suture into the anterior chamber, creating a trabeculotomy (removal of the TM and inner wall of Schlemm's canal). Sharkawi's prospective study of 103 PXFG eyes showed a mean baseline IOP of 27.1 mmHg (95% CI 25.5 to 28.7) using 2.9 (SD 1.1) glaucoma medications, respectively, which decreased postoperatively to 13.0 mmHg (95% CI 11.5 to 14.4) and 1.0 (SD 1.1) medications at 24 months. Roughly half of the eyes underwent cataract surgery followed immediately by GATT; the other half had GATT only, with no ultimate difference in effect between the two groups.⁹⁸ Ozkart's retrospective, non-randomized study of 66 PXFG eyes reported a 25.35 ± 8.52 mmHg mean pre-op IOP decreasing to a 14.65 ± 5.21 mmHg late post-op IOP at an average follow-up of 19 ± 6.12 months.⁹⁹ Aktas' retrospective study of 111 PXFG eyes showed a pre-operative baseline IOP of 26.1 mmHg (SD 7.4) and post-operative IOP of 12.3 mmHg (SD 3.2) at 12 months and 13.2 mmHg (SD 3.1) at 36 months.¹⁰⁰ Both Bozkart and Aktas also had POAG groups with no ultimate difference in treatment effect/success between PXFG and POAG. Aktas noted a greater effect of treatment in PXFG (versus POAG) in the first post-operative year, possibly due to washout of exfoliative debris from the rest of the anterior segment in addition to removal of the trabecular-exfoliative obstruction site. These authors also observed that cataract surgery did not have an additional IOP-lowering effect versus GATT alone. Complication and re-operation rates for necessary further IOP-lowering were not significantly different between the POAG and PXFG eyes.⁹⁹⁻¹⁰⁰ The most common complication of GATT was hyphema, which occurred in roughly one-third of PXFG eyes in Aktas's study. However, this does not usually require anterior chamber washout.¹⁰⁰

The Xen 45 Gel implant (Allergan, Dublin, Ireland) is a 6 mm-long, 45 μ m-diameter porcine-gelatin tube inserted ab interno from the anterior chamber to the subconjunctival space. It is supposed to be safer than trabeculectomy as it does not require a conjunctival dissection, cutting of a scleral flap, or iridectomy. Moreover, its 45 μ m diameter was specifically chosen to reduce the risk of hypotony.¹⁰¹ A 2022 systematic review (including 3 studies of 118 total PXFG eyes) showed a significant treatment effect in both POAG and PXFG, with no significant difference between the two groups.¹⁰² In a prospective study of 53 PXFG eyes with no disclosed connections to Allergan, Mansouri showed that the baseline mean IOP dropped from 19.7 ± 8.2 mmHg to 13.6 ± 4.3 mmHg at 12 months. The mean number of medications was significantly reduced from 2.0 ± 1.3 preoperatively to 0.5 ± 0.8 . Thirty-eight percent of the PXFG eyes required at least one bleb re-needling to remove filtration-device adhesions. Unfortunately, the avoidance of a conjunctival incision means that the lumen of the XEN can be easily blocked by Tenon's capsule; this may partly explain the higher frequency of bleb revision required versus trabeculectomy.¹⁰³ The IOP-lowering effect of Xen appears to decrease over time, while Gillmann found that PXFG eyes require revision sooner (average of 135 days) than POAG eyes (163 days), though this difference was not statistically significant. The authors postulated that more inflammation and blood aqueous barrier disruption associated with PXFG leads to increased post-surgical scarring.¹⁰⁴

Trabeculectomy and tube shunts for PXFG

Trabeculectomy is a filtering surgery in which a passageway is created from the sclera (sclerostomy) into the anterior chamber. A half-thickness scleral flap is loosely sutured on top of this passageway to prevent excessive aqueous loss that could result in hypotony. The aqueous flows through this scleral flap into the subconjunctival space, which leads to an aqueous humor-filled elevation of the conjunctiva, referred to as a filtering bleb. Mitomycin C is an antimetabolite used during trabeculectomy to prevent multiplication of cells that produce scar tissue, which in turn may retard aqueous drainage.¹⁰⁵ In open or closed angle recalcitrant PXFG, trabeculectomy can be performed alone or combined with cataract surgery when physiologic TM functionality, patient compliance and/or ability to afford medications is questioned enough to merit the potential complications/risks.¹⁰ Two

prospective studies on over 70 PXFG eyes receiving trabeculectomy showed a combined average IOP reduction of just over 14 mmHg for a follow-up duration of roughly 26 months.^{106,107} Greater destruction of the blood aqueous barrier is seen after trabeculectomy in PXF eyes (versus POAG) with resultant inflammatory cytokines and exfoliative material itself theoretically contributing to increased formation of bleb scarring. PXFG eyes thus may be at higher risk of complications and long-term failure after trabeculectomy than POAG eyes.^{107,108} In a retrospective study of roughly 50 PXFG and 75 POAG eyes, Li found significantly lower success of IOP reduction at 3 and 5 years in the PXFG group.¹⁰⁹ Interestingly, Rao found comparable results in PXFG eyes that underwent cataract surgery *alone* with regard to final acuity, long-term IOP profile and visual field progression versus cataract/trabeculectomy combined. Unfortunately, Rao's sample size was small and the study was retrospective, and thus may have been prone to a selection bias.¹¹⁰

Glaucoma drainage devices (GDD), otherwise known as tube shunts, carry aqueous humor from the anterior chamber to an external conjunctival reservoir, where a fibrous capsule forms roughly 4-6 weeks after surgery and subsequently regulates flow.¹¹¹ The *Primary Tube Versus Trabeculectomy* study showed that tube shunts had a similar end-point IOP and number of medications at 3 years with a significantly lower chance of failure and post-operative complications compared to trabeculectomy. Compared to 7% in the trabeculectomy group, only 1% of tube shunt patients suffered serious complications at 1 year of follow-up that resulted in loss of two Snellen lines or need for repeat surgery. However, PXFG patients comprised only 4% of the cohort in this trial and a subgroup analysis was not available.¹¹² Thus, at present, there is limited large-cohort PXFG-specific evidence for GDD.¹⁰⁸ A large retrospective case series categorized PXFG as a risk factor for tube erosion.¹¹³ Corneal endothelial health is another area of potential further study that is relevant in PXFG, since both GDD and PXF have been *independently* associated with reduced endothelial cell density.¹¹⁴⁻¹¹⁶ Promisingly, Nobl found that MicroShunt® GDD (Glaukos) implantation had similar efficacy in eyes with POAG and PXFG, which showed IOP reductions from 21.5±5.8mmHg to 12.8±3.0mmHg and reductions in the number of medications from 2.8±1.3 to 0.3±0.8 at 12 months. However, this was a small study. Higher rates of transient hypotony and choroidal detachment were also observed in PXFG eyes. Corneal endothelial cell count testing was apparently not performed.¹¹⁷

CONCLUSION

Pseudo-exfoliation glaucoma features greater IOP fluctuations and is more refractory to topical treatment than primary open angle glaucoma. Based on the literature reviewed here, agents can be added to prostaglandin first-line monotherapy to better control the increase in IOP and the tendency for progressive glaucomatous loss. Furthermore, the encouragement of timely selective laser trabeculoplasty and/or various microinvasive glaucoma procedures in PXFG is supported by the literature when compliance, tolerance and/or progression mean that topical therapy by itself may not be appropriate. Studies have shown that cataract surgery in cases of PXFG is highly effective at lowering IOP, possibly due to washout of exfoliative material from the anterior chamber and trabecular meshwork. Cataract surgery may also reduce the liberation of pigment and exfoliative material by reducing chaffing of the anterior lens capsule against the posterior iris. Furthermore, as many patients with PXF have occludable angles, earlier cataract surgery or laser peripheral iridotomy is likely to be useful for eliminating an angle closure component, though admittedly both of these procedures have risks that are magnified in PXF, including zonulopathy, endothelial cell loss and inflammation. Additional unbiased, long-term, large-sample prospective studies are needed to reveal which MIGS and glaucoma drainage devices are most effective and safe in PXFG. In particular, studies are needed on drainage/tube devices in PXFG. So far in the literature, the relative safety and still impressive effectiveness of MIGS for TM removal including trabectome surgery and especially GATT might sway a clinician to recommend this over trabeculectomy, at least initially. Gonioscopy-assisted transluminal trabeculotomy in particular has been shown to give good results in cases of PXFG, both alone and combined with cataract surgery, though further studies are needed on all these procedures in this aggressive glaucoma subtype. ●

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