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Chapter

Management of Secondary Glaucoma, a Rising Challenge

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Abstract

Secondary glaucoma has increased exponentially in recent times. This is partially due to the increase in complex eye surgeries like corneal transplantation and vitreoretinal surgery and partly due to the increase in life style related diseases like diabetes causing an increase in the prevalence of neovascular glaucoma. The other leading causes of secondary glaucoma are post-trauma, post-cataract surgery, and lens-induced glaucoma. Secondary glaucoma is an important cause of visual morbidity. The management of this complex glaucoma is difficult as they are mostly intractable and do not respond to anti-glaucoma medications. Many patients who are not managed by medical management may require surgical intervention along with vigilant control of their primary pathology. This course would address the stepwise approach to the management of these glaucomas and the tips and tricks to tackle the nuances during management. This chapter would specifically address the management of neovascular glaucoma, Post-PK glaucoma, lens-induced glaucoma, traumatic glaucoma, and uveitic glaucoma.

Keywords: secondary glaucoma, neovascular glaucoma, lens induced glaucoma, uveitic glaucoma, traumatic glaucoma

1. Introduction

Any form of glaucoma with an identifiable cause of increased intraocular pressure, leading to optic nerve damage is referred to as secondary glaucoma. Being acquired conditions, they tend to have a unilateral presentation and the underlying pathology may be that of an open or closed-angle glaucoma. The leading causes of secondary glaucoma were found to be neovascular glaucoma, trauma, post-keratoplasty, uveitic glaucoma, and lens-induced glaucoma.

2. Post PK glaucoma

2.1 Introduction

Penetrating Keratoplasty (PK) involves resecting the host cornea and replacing it with a full-thickness donor graft. In 1969, Irwin and Kaufmann first reported the high

incidence of increased IOP following PK [1]. They reported a mean maximum pressure of 40 mmHg in aphakic and 50 mmHg in combined transplants and cataract extraction in the immediate postoperative period. Since then, various authors have reported the incidence of glaucoma in the early postoperative period from 9 to 31 % [2–4] and from 18 to 35 % in the late postoperative period [5, 6]. One of the reasons for this great variation in incidence is the different manner in which glaucoma after PK is defined in various studies [7]. In fact two leading causes of graft failure Post PK are Graft rejection and Secondary Glaucoma. Graft rejection following glaucoma is the second leading cause of graft failure [8]. Glaucoma following keratoplasty can be defined as an increase in the intraocular pressure (IOP) above 21 mmHg with or without associated alteration in visual fields or optic nerve changes that necessitates treatment [9, 10].

Post Penetrating Keratoplasty glaucoma (PPKG) occurs with increased incidence in patients with preoperative glaucoma. Simmons et al noted PPKG in 34% of 229 patients, out of whom 27% had preoperative controlled glaucoma [11]. In another study by Thoft et al, only 10% of patients presenting with PPKG did not have preoperative glaucoma [12].

PPKG is one of the most challenging problems because of its frequent occurrence, difficult diagnosis and monitoring, complexity of its management, irreversible visual loss due to damage to the optic nerve as well as the donor endothelium [5]. Diagnostic difficulty arises due the errors in tonometry recordings of a thick/astigmatic corneal graft [13]. In addition, it is often not possible to assess adequately the optic nerve/visual field before surgery/in the immediate postoperative period because of preoperative media opacification and corneal distortion with high astigmatism [14]. Timely management and diagnosis of post-PK glaucoma with the initiation of appropriate treatment is mandatory to preserve optimal graft clarity and ONH function [15].

2.2 Etiology and risk factors

PK is complicated by a significant incidence of IOP elevation in both the early and late postoperative periods. Early presentation tends to occur within the first few weeks after surgery [16]. Late postoperative period tends to occur >3 months [16]. Pre-existing glaucoma predisposes to increased IOP post-keratoplasty and can become the culprit early/ late following surgery [17].

The most significant risk factors (**Table 1**) noted were pre-existing glaucoma, lens status (i.e. aphakia, pseudophakia), and the disease for which PK is performed [19]. On comparing the incidence of PPKG in phakic, pseudophakic, and aphakic groups, Hemanth et al found that the aphakic group had the highest risk, followed by the pseudophakic and phakic groups; however, there was no statistically significant difference between the last two groups [20]. Kirkness and Ficker published one of the largest studies on the incidence and risk factors associated with post-PK glaucoma, which included 1122 PKs, performed at Moorfields Eye Hospital, London. The incidence of post-PK glaucoma was 14%. Corneal dystrophies and keratoconus had the lowest risk of glaucoma, contrary to bullous keratopathy, anterior segment trauma, iridocorneal endothelial syndrome, and corneal perforations which had an increased risk [21, 22]. In another study, Kirkness and Mashegov demonstrated an increased incidence of post-PK glaucoma after corneal perforations, especially those after bacterial ulcers, was due to the formation of peripheral anterior synechiae (PAS)

Recipient >60 years
Aph akic and Pseudophakic Bullous Keratopathy [4]
Preexisting glaucoma [3]
Adherent leucoma
Herpes virus infection
Trauma [4]
Repeat PK [18]
ICE syndrome
Perforated corneal ulcer [18]
Combined PK and cataract extraction
Performance of vitrectomy during PK
Anterior segment reconstruction

Table 1.
Risk factors for glaucoma in patients undergoing PK.

Viral keratitis [3]	20–75%
ABK [2]	20–70%
Peters Anamaly [5]	60%
Aniridia [5]	56%
Trauma [6]	9–55%
Pseudophakia [3]	18–53%
Ulcerative diseases	50%
Corneal Regraft [2]	45–50%
Fuchs Dystrophy [5]	0–37%
Kertaoconus [18]	0–12%
CHED & ICE [18]	0–3%

Table 2.
Rates of chronic post PK glaucoma.

and secondary angle closure. The longer the period between the perforation and the transplant, the higher the risk of glaucoma [23].

From **Table 2**, it can be seen that the rates of chronic glaucoma after PK differ significantly based on the indication for PK (from a low of 0–12% for keratoconus to a high of 75% after infectious keratitis).

2.3 Pathophysiology

The pathophysiology of post-PK glaucoma is multifactorial, the causes being compression of the angle's anatomical elements with the trabecular meshwork's (TM) collapse, incorrect suturing of the graft, postoperative inflammation, and prolonged use of corticosteroids in the postoperative period (**Tables 3–6**).

a) Tight suturing
b) Long bites (more compressed tissue)
c) Larger trephine sizes
d) Smaller recipient corneal diameter
e) Increased peripheral corneal thickness

Table 3.
Factors contributing to angle distortion.

a) Less tight sutures
b) Deep sutures
c) Short sutures
d) Suture bites equal on either side of wound
e) Smaller sized grafts
f) Donor corneas larger than that of the recipient
g) Thinner recipient corneas
h) Larger overall corneal diameter

Table 4.
Factors decreasing angle compression.

Early onset	**Intermediate onset**	**Late onset**
a) Viscoelastic induced	a) Vitreous in AC	a) POAG
b) Trabecular collapse	b) Hyphema	b) Ghost cell
c) Preexisting OAG	c) Inflammation	c) Epithelial ingrowth
d) Inflammation	d) Steriod induced	d) Steriod induced
e) Hyphema	e) Ghost cell	e) Rejection/inflammation SEQ
	f) Graft rejection	

Table 5.
Mechanism of raised IOP after PK open angle glaucoma.

Early onset	**Intermediate onset**
a) Preexisting PAS	a) Puppilary block
b) Wound leal with angle closure	b) Malignant glaucoma
c) Operative technique causing compression	c) Progressive synechial closure
d) Puppilary block	
e) Malignant glaucoma	

Table 6.
Mechanism of raised IOP after PK angle closure glaucoma.

Olson and Kaufman [6], using a mathematical model, proposed that the elevated IOP following PK in an aphakic patient might be the result of angle distortion secondary to a compressed tissue in the angle. Edema and inflammation after surgery lead to further compromise in the TM function, and the situation is further aggravated by angle distortion.

2.4 Viscoelastic induced

Viscoelastic material is applied in PK procedures in order to ensure maintaining a physical depth between the posterior transplanted cornea and underlying structures including the iris and the lens [24]. The viscoelastic material also decreases the risk of mechanical injury to structures. As much as it is essential to maintain corneal graft survival, the viscoelastic substance is associated with an increased incidence of post-PKP glaucoma [25]. The viscoelastic's high viscosity can cause trabecular meshwork (TM) obstruction, thus hindering aqueous humor outflow from the anterior chamber (AC) [26]. A study conducted by Hozler et al. showed a direct association between increased viscoelastic substance viscosity and increased IOP, but there was no statistical significance [27]. Retained viscoelastic material in the anterior chamber is the most common cause of IOP rise in the immediate post-operative period [28]. Complete removal of viscoelastic should be done at the end of surgery.

2.5 Suturing technique and transplant size

Tight sutures between the recipient and donor tissues would lead to straitening of the two, thus decreasing the corneo-limbal angle and the corneal curvature. This in turn would increase the risk of iridocorneal angle collapse, PAS formation, and out flow obstruction [29–31]. This can be further understood from **Figure 1**. Angle α represents the ideal iridocorneal angle after PK, whereas β is the angle when tight sutures are applied and θ is the difference between the two. More the θ, the more the chance of PPKG. Usually, a combination of same-sized donor button [32], tight sutures, and long bites causes angle crowding that can compromise the TM.

Zimmerman et al demonstrated how through-and-through sutures decreased the aqueous outflow to a lesser extent when compared with mid-stromal sutures (by a

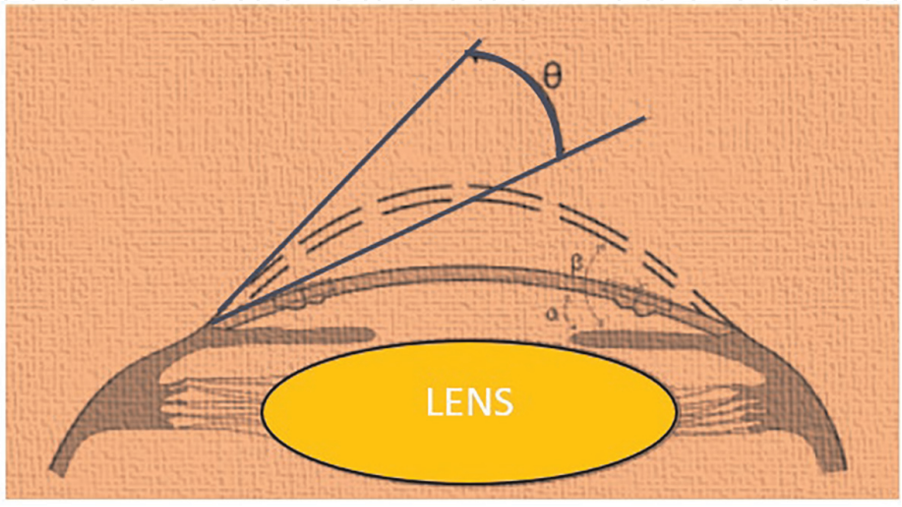

Figure 1.
Effect of suturing technique on development of PPKG.

factor of 37%) in aphakic patients. In phakic patients, the aqueous outflow did not depend on the depth of sutures, according to their study [33]. They speculated that through-and-through sutures prevented retraction of Descemet's membrane and played a role in keeping the angle taut.

Olson and Kaufmann suggested that the development of PPKG can be avoided by appropriate manipulation of the host and donor sizes [34]. It has been proposed to use a donor button 0.5 mm larger than the host bed. Oversized graft buttons were found to have better control when compared to same-sized buttons in eyes with no pre-existing glaucoma.

Moreover, oversized grafts provide optimal AC depth, which reduces the risk of PAS formation and resultant IOP spike.

2.6 Inflammation and PAS

Late onset post-PK glaucoma is usually due to synechial angle closure with the degree of PAS strongly correlating with the need for surgery. PAS occurs more commonly in eyes undergoing PK for suppurative keratitis and perforated ulcers. In failed, opaque grafts Dada et al concluded that PAS formation was an important cause of secondary angle closure glaucoma post PK [35]. It was also noted that pupilloplasty and iris suturing during keratoplasty decreased the PAS formation [36].

A study by Vajpayee et al. observed that grafts oversized by 1 mm decreased the risk of iridocorneal adhesions [37]. Also, those with pre-existing iridocorneal adhesions were at an increased risk of developing PAS postoperatively in spite of adequate suturing and synechiolysis.

2.7 Corticosteroid usage

Steroids are essential in the postoperative period to prevent endothelial rejection and maintain graft survival. However, steroids themselves are known to cause glaucoma by multiple mechanisms like water retention, inhibition of phagocytic properties, accumulation of cellular debris, and glycosaminoglycans [38–40]. It is known to account for 20–70% of PPKG in different studies [41–44]. The steroid-induced rise in IOP post-PK occurs more commonly in patients with keratoconus and Fuch's Dystrophy (73% and 60.3%, respectively) [25]. It has been suggested to decrease the steroid therapy to the minimum possible to control the IOP spikes [12].

A study done by Mindel et al noted the tendency of different steroids to induce IOP spike over a six-week period. Dexamethasone increased the IOP twice as much as fluorometholone and eight times as much as medrysone [45]. While difluprednate 0.05% was shown to have an IOP rise in 21% of cases [46], fluorometholone and rimexolone caused less IOP elevation but also have decreased anti-inflammatory effects [47]. The efficacy of Cyclosporine A alone to control inflammation and suppress post-PK rejection remains to be determined [48].

2.8 Diagnosis

It is difficult to establish a starting point for the postoperative period because measuring the IOP, optic disc and visual field evaluation are on most occasions difficult to perform preoperatively due to primary corneal disease. After PK, changes

in corneal thickness, postoperative astigmatism, and refractive changes often preclude adequate evaluation of the IOP, optic disc, and visual field.

The diagnosis of glaucoma post-PK is primarily based on the IOP measurement in the early postoperative period and on IOP, optic disc changes, and progressive visual field changes in the late postoperative period. In the postoperative period, IOP can be measured especially when the cornea is irregular with a tonopen/ mackaymarg tonometer [49] or a Dynamic contour tonometer (DCT) which works independently of the corneal thickness.

Multiple studies compared DCT with GAT in cases with keratoplasty and proved that DCT was not influenced by thickness, curvature, and corneal astigmatism [50–52]. GAT underestimates the pressure reading post-PK [50, 53]. Kandarakis at al. reported an average IOP measurement by DCT to be 16.6 (SD 2.8) mmHg, while that obtained by GAT to be 15.1 (SD 3.6) mmHg.

On comparing the I-care tonometer with GAT, the values were found to be similar in cases of anterior and posterior lamellar keratoplasty, but in PK patients, I-care underestimated the IOP compared to GAT [54].

The accuracy of GAT is reduced in the presence of corneal edema (underestimation of IOP), corneal scars (overestimation of IOP), blood staining, or any condition which alters corneal thickness or elasticity.

Another device to measure IOP is Ocular Response Analyzer (ORA) which also measures corneal hysteresis, thus taking corneal biomechanical properties into account while measuring IOP. Studies have noted a considerably wide difference in IOP measurements with ORA when compared with GAT [55, 56]. Chou et al. showed a mean of 6.29 mmHg higher reading of IOP with ORA than with GAT. This indicates the need for an adjusted coefficient for GAT IOP reading to become more reliable.

In the presence of tarsorrhaphy, digital palpation [57] can be used or new tonometers which measure the IOP through the lid (Proview Phosphene tonometer) can be used.

PAS formation causing secondary angle closure is an important etiology of raised IOP post-keratoplasty in patients with totally opaque grafts [35]. UBM can be used to view the angle and find the cause of the Post-PK Glaucoma, especially in eyes with a failed graft where the anterior segment details are not visible. The extent of iridocorneal adhesions, the location of IOL, phakic/aphakic status, AC depth, Angle width, and corneal thickness can be determined by UBM. It also helps the glaucoma surgeon in planning the site for a trabeculectomy or a glaucoma drainage device.

2.9 Management

Management of Post-PK Glaucoma is a challenging affair and various steps need to be taken during the surgery to prevent this blinding condition.

2.9.1 Prophylaxis

A. Preoperative factors

Preexisting glaucoma should be well-controlled prior to the surgical intervention. If the IOP is difficult to control with drugs or if the control imposes maximal therapy, the IOP can cause decompensation after keratoplasty. Therefore, in these cases, glaucoma should be controlled surgically and a transplant should be performed afterward [5] because multiple studies revealed a higher incidence of graft failure if the

intervention for glaucoma was performed after keratoplasty [18]. Some studies recommend trabeculectomy with mitomycin C (MMC) application or with a GDD concomitantly with PK [18–20].

B. INTRAOPERATIVE FACTORS – During Surgery, the use of the following procedures reduces the risk of Post PK glaucoma

1. 1mm oversize donor corneal button
2. Deep, short, adequately tight bites
3. Goniosynechiolysis
4. Iridoplasty procedures (in cases of atrophic iris)
5. Viscoelastic removal at the end of surgery
6. Careful wound closure to prevent postoperative wound leaks

C. Postoperative factors

1. Judicious use of topical steroids controls PAS and inflammation.
2. Cycloplegics keep the pupil mobile and prevent pupillary block glaucoma.
3. Monitoring of IOP as long-term use of steroids can cause secondary open-angle glaucoma.

2.9.2 Medical management

The use of topical anti-glaucoma medication is still the first line of treatment to control post-PK glaucoma. Beta-blockers, alpha-2 agonists, carbonic anhydrase inhibitors (CAI), topical prostaglandin analogs, miotics, rho-kinase inhibitors as well as systemic CAI can be used to treat post-PK glaucoma.

Adrenergic agents are not used much as they cause chronic conjunctival inflammation. Miotics have little effect in the presence of PAS in cases of angle closure, so they are also not much used. Systemic CAI is very useful as a short-term therapy in the early postoperative period. Long-term therapy is limited by serious side effects such as tinnitus, nausea, gastrointestinal disturbances, paraesthesia, depression, anxiety, weight loss, nephrolithiasis, and blood dyscrasias. Topical CAI should be used with caution as they suppress carbonic anhydrase enzyme in the corneal endothelium and long-term use can lead to graft rejection.

Preservatives such as benzalkonium chloride are epitheliotoxic and one should avoid and use preservative-free unims for long-term therapy.

When using topical anti-glaucoma medication, one has to be aware of the local side effects of the drugs as these side effects can be detrimental to the state of the graft.

In the cases of steroid-induced glaucoma, the dose of steroids should be tapered to the minimum possible dose. High-potency steroids should be replaced with low-potency steroids such as fluorometholone and loteprednol. Cyclosporine 0.5–2% can be substituted for steroids and this can help in IOP control.

2.9.3 Laser therapy

Selective/ Argon laser trabeculoplasty (SLT/ALT) has been used quite infrequently in this subset of patients. There are few reports indicating a significant reduction with laser trabeculoplasty in areas of the angle without PAS [58, 59]. Van Meter et al. reported an average IOP reduction of 9.1 mm Hg in 10 patients with ALT persisting till a follow-up of two years [58].

2.9.4 Surgical management

Surgical options include trabeculectomy with mitomycin C, glaucoma drainage devices, and cyclophotocoagulation. Ayyala et al reported no significant difference in IOP control and graft failure when comparing the above three procedures [60]. Sekhar et al. reported a preference for trabeculectomy in phakic eyes because of higher success in a patient with a previously undisturbed angle. Endothelial cell loss is also reported to be negligible compared to Ahmed valves [61]. Overall, the success rates for IOP control range from 87% (14 of 16 eyes) with 1-year follow-up to 50% (12 of 24 eyes) after 2 years of follow-up based on various small studies [62, 63]. Graft clarity has been reported to be 60% after 2 years in a series of 24 patients and 62% after 22 months in a series of 26 patients [63, 64]. Glaucoma drainage implants (GDIs) are possibly the most successful modality for control of IOP after the fewest treatment procedures [65]. IOP control has been reported to be 62–96% after 2 years of follow-up [66, 67]. The rate of graft failure has been reported to be 35–74% after 2 years of follow-up [68, 69]. The tube of these devices can be placed in the anterior chamber (AC), posterior chamber (ciliary sulcus), or in the anterior vitreous via the pars plana route. Placing the tube in the AC has been associated with an increased risk of corneal endothelial damage and decompensation, with the reported frequency between 7% and 27%. Pars plana insertion would require additional vitreoretinal surgery and thus pose an increased risk of retinal damage. Rumelt and Rehany reported a safer alternative technique of tube insertion into the ciliary sulcus in patients with glaucoma secondary to corneal transplantation [70].

For eyes with intractable glaucoma and poor visual potential, cyclodestructive modalities have been advocated.

3. Lens induced glaucoma

Lens induced glaucoma (LIG) is a common form of secondary glaucoma in which the crystalline lens is involved in the mechanism of raised IOP. It was first reported by two clinicians independently; Gifford and von Reuss [71]. Later various workers described such types of cases under different names like LIG, lens-induced uveitis and glaucoma, phacotoxic glaucoma, phacogenic glaucoma, phacolytic glaucoma etc. At present, LIG is a clinical condition characterized by

- a violent secondary glaucoma (resembling acute angle closure glaucoma) in one eye with a senile mature cataract, hyper mature senile cataract (rarely immature senile cataract)
- normal intraocular pressure and open angle in other eye,
- and prompt relief of symptoms and restoration of vision after cataract extraction in the affected eye

The late reporting for treatment of cataracts thus leads to serious complications like LIG and it remains one of the most important causes of irreversible loss of vision, especially so in the rural population.

3.1 Epidemiology

The epidemiology varies across developed and developing countries. In developing countries with more limited resources, acquired LIG from advanced senile cataracts is the more prevalent subtype. The incidence of LIG is up to 2.4% at the time of the presentation of senile cataracts with a female preponderance [72].

3.2 Classification

LIG can be classified into the following subtypes based on their pathogenesis:

1. Lens protein-related: Leakage of lens protein across an intact or a breached lens capsule.

   This form includes

   - Phacolytic glaucoma (PLG)
   - Lens-particle induced glaucoma (LPIG)
   - Phacoanaphylactic glaucoma (PAG)

2. Secondary angle closure: Anatomical obstruction of aqueous flow from the posterior to the anterior chamber

   - Phacomorphic glaucoma (PMG)

3.3 Phacolytic glaucoma

Phacolytic glaucoma was first described by Flocks and colleagues [73]. The condition occurs chiefly in the setting of a senile hypermature, or Morgagnian, cataract with leakage of lenticular material through microscopic openings in an apparently intact lens capsule. The raised IOP was originally thought to be caused by obstruction of the trabecular meshwork by macrophages distended by engulfed lens material and Morgagnian fluid that had escaped from an intact crystalline lens. Later much of the evidence showed the role of high-molecular-weight soluble lens protein, leaked from an intact capsule, in causing direct obstruction of aqueous outflow channels and thus elevation of the IOP. In very rare scenarios, the cataract may be immature, with the liquefaction of the posterior cortex.

3.3.1 Clinical features

Patients present with sudden onset of severe pain and redness of the eye with a history of a gradual decrease in vision over a few months to years. They may complain

of a further acute reduction of vision, usually due to the corneal edema due to the high IOP.

On examination, the presenting signs are high IOP, microcystic corneal edema, and open angles on gonioscopy with few scattered endothelial precipitates. The cellular reaction is usually present in the anterior chamber ranging from mild cells and flare to intense reaction with pseudohypopyon. The cells are usually larger than those seen in other uveitis, as the cells are swollen macrophages with the engulfed lenticular matter.

Diagnosis: Phacolytic glaucoma is usually a clinical diagnosis, but microscopic examination of aspirated anterior chamber fluid can aid in suspected cases. Biochemical studies can help to identify high-molecular-weight lens proteins that have leaked out of the cataract. Engorged macrophages may be seen as well [74].

3.3.2 Treatment

Phacolytic glaucoma is a surgical semi-emergency. After decreasing the inflammation and IOP with topical steroids and topical and oral anti-glaucoma medications, the patient should be posted for cataract surgery removal ideally within a week. Cycloplegic agents aid in decreasing inflammation and pain. Usually, miotics and prostaglandin analogs are avoided in anti-glaucoma therapy for these conditions, due to their pro-inflammatory roles.

Cataract extraction can be done by ECCE, SICS, or phacoemulsification depending upon the surgeon's expertise. Even in patients presenting with No Perception of light, cataract surgery can be performed to decrease inflammation, IOP, and pain.

3.4. Phacomorphic glaucoma

Phacomorphic glaucoma is a type of secondary glaucoma caused by lens swelling in eyes with mature or intumescent cataracts who otherwise are not predisposed to angle closure [75]. When the lens swells, acute angle closure with pupillary block occurs in the acute phase; in the late phase, it can occur even without pupillary block as a result of forward movement of the peripheral iris. Phacomorphic glaucoma is encountered more commonly in developing countries, where cataracts tend to get neglected by the patient because of the general belief that cataract surgery is neither indicated nor feasible unless the cataract becomes matured or 'ripe'.

Clinical features: The presentation of phacomorphic glaucoma is similar to acute angle-closure glaucoma. Patients may experience severe pain and headache secondary to elevated IOP, blurred vision, perception of halos around lights, nausea, vomiting, bradycardia, and sometimes diaphoresis [76]. Clinical features may include corneal edema, conjunctival injection, and a mid-dilated pupil. The intumescent lens may be observed pushing the iris forward and reducing the anterior chamber depth. The cellular reaction may be present in the anterior chamber, usually mild in nature, with angles typically closed on gonioscopy. The diagnosis is made on the basis of typical clinical features.

Management is similar to that of phacolytic glaucoma, involving initial control of IOP and inflammation followed by cataract surgery. The initial lowering of IOP is commonly done with medical treatment with combinations of topical anti-glaucoma medications (AGM), oral acetazolamide, and intravenous mannitol but it has been documented that in 37.5% of cases medical treatment had failed to lower IOP [77].

This may be because of the poor corneal drug penetration and relative ischemia caused by raised IOP leading to the failure of topical therapy. IOP lowering is however desired to prevent the risks of operating on an eye with corneal edema and high IOP.

Cataract surgery in these patients poses several challenges: the high IOP, sometimes quite refractory to medical management increases the risk of posterior capsular rupture and expulsive hemorrhage. The pre-existing corneal haze and shallow AC further increase the risk. The increased intra-lenticular pressure makes anterior capsulotomy difficult, with a high chance of extension or an Argentinian Flag Sign. Formation of the Anterior chamber with a high viscosity OVD and aspirating fluid from the lenticule through a small opening in the anterior capsule decreases the intralenticular pressure and allows a more controlled capsulorrhexis. Different techniques of performing capsulorrhexis have been described in literature like two-step capsulorrhexis, sewing needle microcapsulotomy, phaco-capsulotomy etc.

Role of laser peripheral iridotomy (LPI) Preoperative laser peripheral iridotomy (LPI) may offer multiple benefits in such patients. LPI helps in lowering IOP by releasing the pupillary block and may facilitate surgery by increasing the peripheral AC depth. Moreover, by equalizing the pressures in anterior and posterior chambers the effect of relative ischemia is negated allowing the topical medications to work. But doing an LPI in such patients may be challenging. Corneal edema due to raised IOP may hamper visibility. As the lens is positioned in close proximity to the iris there is a risk of lens capsule rupture with subsequent leakage of lenticular material into the AC.

Although these patients present early to the hospitals because of the acute symptoms, the visual prognosis remains unpredictable due to the irreversible optic nerve damage that may have incurred in a matter of few days. Also, a delay in the treatment causes a permanent synechial closure of the anterior chamber angle as a result of which IOP spikes can be seen even after cataract extraction.

3.5 Lens particle glaucoma

Lens-particle-induced glaucoma was previously mislabelled as 'phacotoxic uveitis'. In lens-particle glaucoma, IOP elevation is caused by obstruction of aqueous outflow by lens particles, which can occur either after cataract surgery (with retained cortical matter/ epinuclear matter), trauma to lens, or YAG posterior capsulotomy.

It is a type of secondary open-angle glaucoma similar to phacolytic glaucoma, the difference being that the lens capsule is grossly disrupted instead of micro ruptures present in phacolytic glaucoma.

Clinical features: Clinical findings of lens-particle glaucoma are similar to those of phacolytic glaucoma with conjunctival injection, corneal edema, elevated IOP, and anterior chamber reaction. However, lens particles cause more inflammation, usually leading to anterior and posterior synechiae and pupillary membranes.

Diagnosis: The diagnosis of lens-particle glaucoma can be made based on a history of recent intraocular surgery or trauma, along with the presence of gross lens material in the anterior chamber.

Treatment: The course of treatment depends upon the severity of the disease upon presentation. If only minimal cortical material is present, cycloplegics, corticosteroids, and IOP lowering agents (aqueous suppressants) usually suffice. However, if there is significant lens matter with high levels of inflammation and poorly controlled IOP, urgent removal of the residual lens cortex is necessary. Prompt treatment is required to avoid serious consequences.

Inflammation persisting for a longer duration can lead to the development of pupillary membranes, pupillary block, and subsequent PAS formation and intractable glaucoma.

Cystoid macular edema and even tractional retinal detachments may also occur.

3.6. Phacoantigenic glaucoma

Also known as Phacoanaphylactic glaucoma, it is the rarest type of lens-induced glaucoma which is often difficult to diagnose. It is an Arthus-type immune complex reaction, mediated by IgG and the complement system against lens proteins. These lens proteins are normally sequestered within the lens capsule and are thus immune-privileged. Either during a complicated cataract surgery involving loss of vitreous or following trauma, these lens proteins get admixed with vitreous and result in retention of these lens proteins followed by their slow release [74]. This usually presents at least after a period of 2 weeks, as this is the time period required for sensitization of the lens protein [78].

3.6.1 Clinical features

Presenting signs include lid edema, conjunctival congestion, corneal stromal/microcystic edema with an intense fibrinous anterior chamber reaction with posterior synechiae with characteristic mutton-fat keratic precipitates. Anterior vitritis also usually occurs. A confirmed diagnosis is established by visualizing the polymorphonuclear leukocytes in the aqueous or vitreous specimen, along with the presence of circulating lens proteins within the aqueous humor. The diagnosis is difficult to establish without aqueous/vitreous tap analysis as the lens proteins seen in the anterior chamber are quite less as compared to the severity of glaucoma.

Treatment: It is similar to other forms of lens-induced glaucoma, involving anti-inflammatory and anti-glaucoma medications and usually requiring surgical removal of the remaining lens material.

3.7 Prognosis of lens induced glaucoma

A good visual prognosis can be expected if the patient presents early and is managed promptly. After controlling the inflammation and IOP, patients should be taken early for surgical management. The presence of PAS post-operatively is associated with a poor prognosis and requires regular IOP monitoring. Usually, the primary surgery involves only cataract extraction or lens matter wash, as trabeculectomy combined at this stage has poor success due to the presence of inflammation at the time of surgery. If IOP remains uncontrolled in the postoperative period on multiple anti-glaucoma medications, then a glaucoma surgery is done.

4. Traumatic glaucoma

4.1 Introduction

Glaucoma is a common complication following trauma. It can occur either after open or closed globe injury.

The 6-month risk of developing glaucoma was estimated to be 2.67% after penetrating injury [79] and 3.4% after blunt injury according to the U.S. Registry [80]. In children <15 years, it is estimated that about 3.3–5.7 million suffer from ocular trauma annually and 160,000–280,000 children/year sustain ocular trauma serious enough to require hospitalization [81].

Risk factors predicting the development of traumatic glaucoma include- elderly, baseline visual acuity < 6/60, elevated baseline IOP, hyphema, angle recession > 180 degrees, iris injury, injury/ displacement of lens [80, 82, 83].

Glaucoma after penetrating injuries is more common in presence of adherent leucoma or lens injury/ displacement [79].

4.2 Closed globe injury

4.2.1 Pathophysiology

Blunt trauma causes momentary anatomic deformation of the globe on impact, leading to sudden posterior displacement of the cornea and anterior sclera and a compensatory expansion at the equator. This can lead to separation at seven rings of tissue anterior to the equator (Rings of Campbell)-

1. Sphincter Pupillae – Radial sphincter tears (**Figure 2**)

2. Trabecular meshwork- Tears/ splits/disruption

3. Iris root – Iridodialysis

4. Split between longitudinal and oblique ciliary muscle – Angle recession

5. Attachment of ciliary body to scleral spur- Cyclodialysis cleft

6. Zonules – Lens displacement

7. Attachment of retina to ora Serrata – Retinal dialysis and detachment

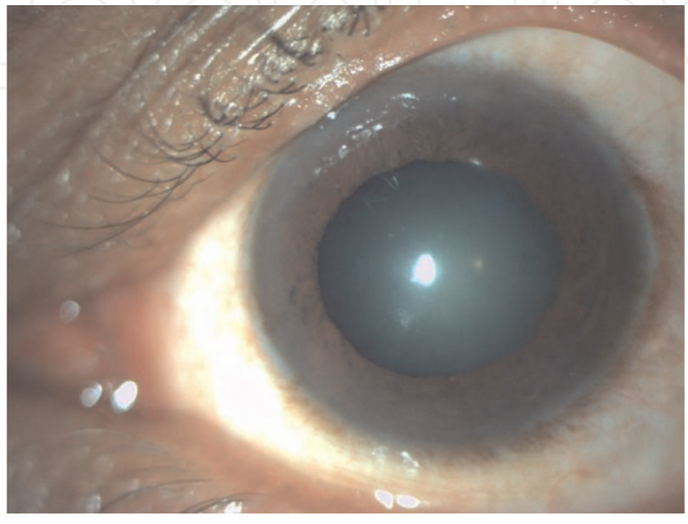

Figure 2.
Multiple sphincter tears causing traumatic mydriasis.

Early onset	Delayed onset
Trabeculitis	Angle recession
Uveitis	Peripheral anterior synechiae
TM disruption	Ghost cell glaucoma
Hyphema	Phacolytic and lens particle glaucoma
Lens-induced glaucoma- Phacomorphic / lens displacement	Delayed closure of a cyclodialysis cleft
Massive choroidal hemorrhage	Rhegmatogenous retinal detachment

Table 7.
Causes of IOP elevation post-ocular trauma.

Causes of IOP elevation post-trauma have been enumerated in **Table 7**.

4.3 Causes of early onset traumatic glaucoma

4.3.1 Trabeculitis and uveitis

Anterior uveitis accounts for 20% of cases of traumatic glaucoma [84]. Subcellular iris and TM trauma trigger an innate immune response, leading to increased vascular permeability and release of inflammatory mediators. Obstruction of the TM by these circulating precipitates or by the primary trabecular swelling can cause an increase in IOP. However, this is self-limiting in nature with the mainstay of treatment being topical steroids and cycloplegic agents.

4.3.2 Trabecular disruption

Acute blunt trauma to the globe can produce partial/full thickness tears in the TM, which lead to hemorrhage in the Schlemm's Canal and scarring over time. They can lead to acute as well as chronic intraocular pressure (IOP) elevation. These changes have been documented in a study when a gonioscopy was performed within 2 days post-injury [85].

4.3.3 Hyphema

The presence of hyphema indicates significant ocular injury. Bleeding most commonly occurs from fine vessels in the angle. The mechanisms by which hyphema can cause glaucoma include- contusion/inflammation of the trabecular meshwork, physical disruption of the meshwork, plugging with red blood cells, or by a large clot in the anterior chamber producing pupillary block.

The extent of bleeding correlates with the incidence of elevated IOP, risk of secondary bleeding, and visual outcomes (**Table 8**) [86–88]. Secondary bleeding is caused by clot lysis and retraction and typically occurs between day 2 and day 7 following the initial injury, during which time close monitoring is advised. Rebleeds are typically worse than the initial bleed and are associated with a worse visual prognosis.

Management is usually conservative in the form of topical and oral steroids, cycloplegic agents, and antiglaucoma medications (other than PGA and miotics). Oral aminocaproic acid and tranexanemic acid have been advocated by few, as they decrease the risk of re-bleeding, however, they are associated with systemic side effects and are known to decrease the rate of clearance of hyphema [89].

Grade of hyphema	Risk of elevated IOP [8]	Chance of recovering vision 20/50 or better [9]	Risk of secondary bleeding [10]
I – 1/3rd of anterior chamber	13.5%	75–90%	25%
II – 1/3–1/2	13.5%	65–70%	
III - >1/2	27%	25–50%	60–70%
IV- Full anterior chamber	50%	25–50%	60–70%

Table 8.
Prognosis depending on the grade of hyphema.

The most commonly cited surgical indications for all patients with hyphema are based largely on two studies done by Read and Goldberg from 1970–1972 [90, 91]. Their surgical indications are:

1. corneal blood staining at any time;

2. total hyphemas with IOP ≥ 50 mmHg for five days to prevent optic atrophy;

3. total hyphemas that do not clear by 50% after six days with an IOP ≥ 25 mmHg (to prevent corneal blood staining);

4. unresolved hyphemas after eight days to prevent PAS; and

5. IOP ≥ 60 mmHg for 48 hours despite intravenous mannitol.

History of sickle cell disease/ trait should be elicited in all patients, particularly those of African American lineage, as these patients experience higher IOP elevation with even minimal hyphema and increase risk of re-bleeds. Goldberg et al recommended surgery (AC wash) in these patients after only 24 hours with a mean IOP ≥ 25 mmHg or several spikes ≥ 30 mmHg [92].

In cases of refractory glaucoma, trabeculectomy has been used to achieve IOP normalization [93, 94].

4.3.4 Massive choroidal hemorrhage

This is a rare cause of acute IOP elevation post-trauma, presenting as a shallow anterior chamber, both centrally and peripherally with a reduced red reflex and choroidal elevation seen on indirect ophthalmoscopy or B scan ultrasonography.

Initial treatment includes topical and oral antiglaucoma medications, cycloplegics, and steroids. Miotics should be avoided as they can cause further anterior chamber shallowing due to ciliary spasms. Persistent angle closure with pressure elevation, lenticulo-corneal touch, and kissing choroidal with retinal apposition warrants surgical drainage.

4.4 Causes of delayed onset traumatic glaucoma

4.4.1 Angle recession

It is defined as the separation between the longitudinal and circular fibers of the ciliary muscle, causing a posterior displacement of the iris root, giving an appearance

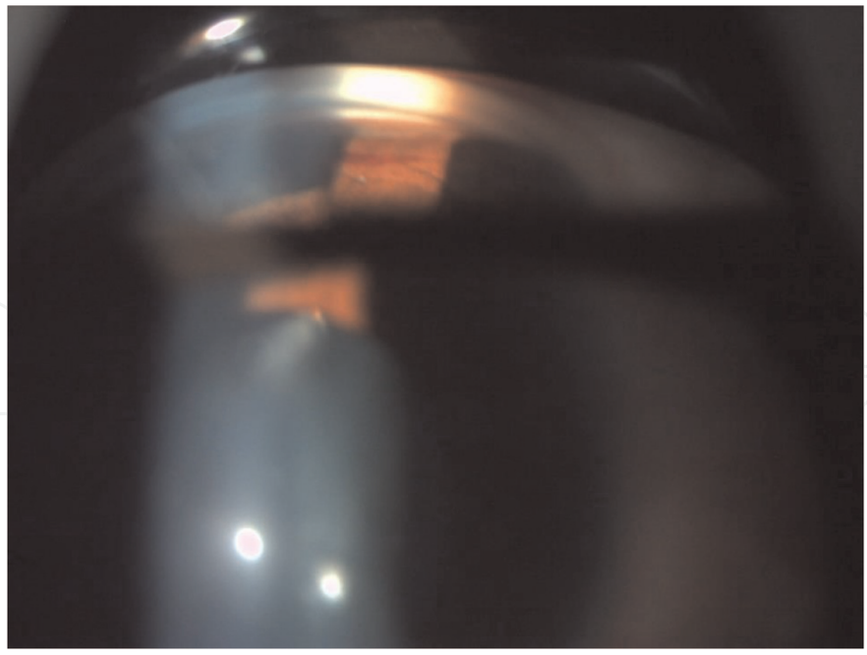

Figure 3.
Angle recession (green arrow) with clotted blood on iris (red arrow).

of widened ciliary body band on gonioscopy. It is indicative of damage to the trabecular meshwork following trauma and is not per se responsible for the increase in intraocular pressure. Its reported incidence ranges from 70 to 100% [95, 96] following traumatic hyphema, however, glaucoma occurs in 7–9% of patients [97]. Glaucoma has been reported to occur either within the first year or after 10 years of trauma [95] with it being more common when angle recession of >180 degrees is present. Spaeth et al reported that 50% of patients with unilateral angle recession glaucoma had frank or probable glaucoma in their fellow eye [97], indicating an inherent predisposition for developing glaucoma in these patients. Treatment is usually medical, with laser trabeculoplasty having some role when IOP is not too high [98]. Refractory glaucoma is treated surgically with either filtering surgery (provided that the conjunctiva is not scarred) or drainage devices. The success of trabeculectomy was found to be lower (43% vs 75%) in these patients when compared to patients with primary open-angle glaucoma [99]. However, routine use of antimetabolites like mitomycin C or 5-FU either intraoperatively or postoperatively has been associated with higher success [100, 101]. A recent study has evaluated the role of AGV implant in angle recession glaucoma with a success of 90% at the mean follow-up duration of 29.47 ± 3.39 months (**Figure 3**) [102].

4.4.2 Peripheral anterior synechiae

Following blunt trauma, the organization of blood and inflammatory debris can lead to either PAS formation or endothelization of the angle. Persistent hyphema for >8 days was found to be associated with PAS formation [91]. Presence of massive choroidal hemorrhage causing AC shallowing can also lead to permanent angle closure. Treatment in these cases often requires surgical therapy, when the IOP is not controlled medically (**Figure 4**).

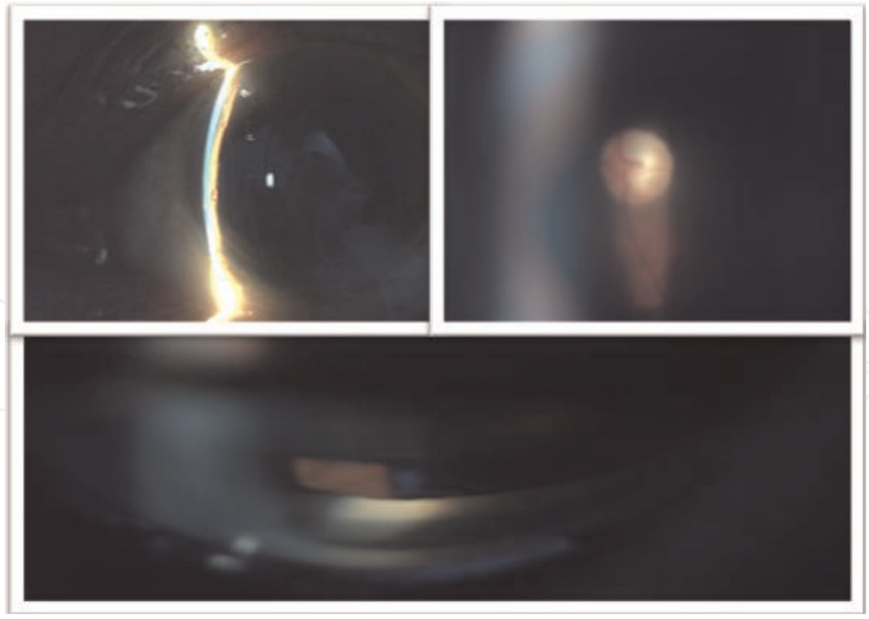

Figure 4.
Secondary angle closure glaucoma following closed globe injury.

4.4.3 Ghost cell glaucoma

Degeneration of red blood cells in an anaerobic chamber like the vitreous leads to the formation of khaki-colored cells, known as ghost cells, as they become depigmented due to the loss of intracellular hemoglobin. Disruption of the anterior hyaloid face after trauma, vitrectomy, cataract surgery, or even spontaneously allows these cells to circulate in the anterior chamber and obstruct the trabecular meshwork due to their rigid nature. This typically occurs 1–3 months after trauma. It is usually self-resolving and managed medically, however, it may require repeated anterior chamber lavage and glaucoma surgery.

4.4.4 Lens-induced glaucoma: can occur in an acute or chronic setting

a. Lens dislocation- Severe trauma can cause zonular disruption and thus anterior or posterior displacement of the lens. Both conditions can cause a pupillary block, either by the lens itself or by vitreous blocking the pupillary margin. Treatment is laser iridotomy/ surgical iridectomy to relieve the pupillary block followed by lensectomy.

b. Lens swelling- Phacomorphic glaucoma: The impact from blunt trauma can cause an immature cataract to become intumescent, causing either pupillary block or a forward push of the iris-lens diaphragm leading to angle closure glaucoma. Treatment is the same as in the above condition.

c. Phacolytic and lens particle glaucoma: Microruptures in the fragile anterior capsule of a hyper mature cataract induced by trauma, cause leakage of high molecular weight proteins into the anterior chamber and clog the trabecular meshwork causing secondary open-angle glaucoma. Similarly, a complete rupture of the anterior capsule will cause leakage of lens fragments which in turn will obstruct the trabecular meshwork. Treatment in both these conditions

is by surgical removal of the lens after decreasing the inflammation and lowering the intraocular pressure medically.

4.4.5 Delayed closure of a cyclodialysis cleft

Closed globe injury may be associated with acute hypotony in some instances. These include severe cyclitis causing ciliary body shutdown or development of a cyclodialysis cleft. Separation of the ciliary muscle from the scleral spur creates this cleft, which acts as an alternative outflow pathway for aqueous humor, causing a decrease in IOP. Over time, this cleft undergoes fibrosis, which may cause an elevation in IOP. Goldmann hypothesized that a decrease in the flow through the conventional trabecular meshwork pathway results in its decreased permeability, and thus it fails to function after the closure of the cleft. Treatment is aimed at controlling the IOP either medically or surgically. Miotics and phenylephrine may be effective in reopening the cleft in the early stages (**Figure 5**).

4.4.6 Rhegmatogenous retinal detachment

The retinal tear usually causes a decrease in IOP due to an increase in the uveoscleral outflow through the tear. In 5–10% of cases, ocular hypertension can occur, possible causes being pre-existing open-angle glaucoma, presence of inflammation and rarely Matsuo-Shwartz Syndrome [103] (obstruction of trabecular meshwork with photoreceptor outer segment cells).

4.5 Open globe injury

Risk factors for developing glaucoma after open globe injury include advancing age, hyphema, lens injury, perforating injury, zone 2 injury, vitreous hemorrhage, lens

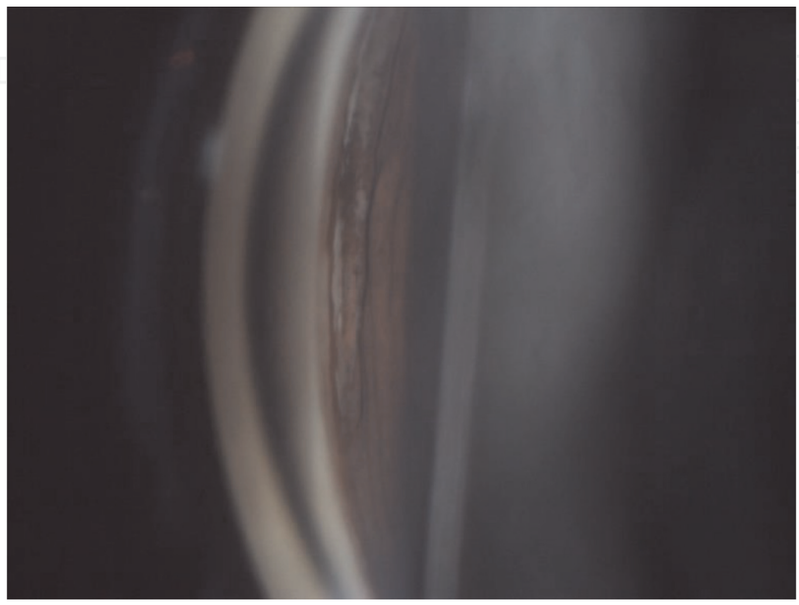

Figure 5.
Cyclodialysis cleft with co-existent angle recession.

dislocation, presence of the intraocular foreign body, and cataract surgery following primary repair. The incidence was found to range from 2.6% to 17% in various studies [104–107].

4.5.1 Causes of glaucoma following open globe injury

Osman et al classified glaucoma after open globe injury into three stages namely early (<1 month), intermediate (1–6 months), late stage (>6 months). They found the cause of glaucoma in the early stage to be un-removed lens particles, inflammation, and hyphema. In the intermediate stage, glaucoma was due to synechial angle closure, ghost cell glaucoma, and unremoved lens particles. In the late stage, the causes noted were angle recession and synechial angle closure [107]. Other causes include epithelial down growth, fibrous ingrowth, and retained intraocular foreign body. A few of these conditions will be discussed subsequently.

A. Epithelial downgrowth

A rare cause of delayed glaucoma following open globe injury, it can present either as epithelial cysts or pearls, or membranes. Risk factors include inadequate wound closure, wound fistula, presence of iris incarceration or vitreous incarceration in a full-thickness wound, and iatrogenic implantation of epithelial cells into the anterior chamber while repairing ocular lacerations. While cysts and pearls, usually do not cause glaucoma, the membrane can obstruct the drainage from the angle, first by growing over it and later by undergoing contraction and causing synechial closure. It appears as a grey translucent membrane with scalloped edges and presents as a retro corneal membrane with corneal edema and glaucoma. Treatment is challenging and aimed at controlling intraocular pressure. Glaucoma drainage devices are preferred due to the high rate of failure with trabeculectomy. In recalcitrant cases, cyclophotocoagulation is often required.

B. Fibrous ingrowth

Presents either as a focal, thick, vascularized membrane inside the anterior chamber or as an extensive membrane covering the corneal endothelium, trabecular meshwork, and iris surface. Glaucoma is usually refractory to medical and surgical treatment and requires cyclodestructive procedures.

C. Retained intraocular foreign body

A retained foreign body can cause ocular hypertension and glaucoma by various mechanisms. Angle-closure glaucoma can occur due to synechiae formation following shallowing or flattening of the anterior chamber after penetrating injury, due to epithelial /fibrous ingrowth or due to pupillary block from an anteriorly dislocated or intumescent lens. Rupture of the anterior lens capsule with the foreign body can cause lens particle glaucoma. A delayed type of glaucoma is siderotic glaucoma, due to fibrosclerosis of trabecular meshwork from the intraocular toxicity of the iron-containing foreign body [108]. These patients have a typical presentation with iris heterochromia, mydriasis, rust-like discoloration of anterior chamber structures, nyctalopia, and reduced electroretinogram responses. The mainstay of management is the removal of the foreign body. Few cases with similar manifestations have been reported without any evidence of an intraocular foreign body. This has been attributed to the iron derived from the degradation of red blood cells in patients with a history of hyphema or vitreous hemorrhage. The hemoglobin from the lysed red blood cells is phagocytosed and degraded into hemosiderin which accumulates in ocular tissues causing degeneration and sclerosis. This has been termed as hemosiderotic glaucoma [109].

5. Uveitic glaucoma

5.1 Introduction

Uveitic glaucoma also known as inflammatory glaucoma is an acquired clinical entity that causes secondary glaucoma. Intraocular inflammation and intraocular pressure share a complex relationship as they can alter both aqueous production as well as its drainage. Inflammation leads to alteration in aqueous composition resulting in increased resistance to outflow, blockage of trabecular outflow facility by cells and debris, structural changes of trabecular meshwork due to corticosteroid use and pupillary block [110]. It is estimated that 38–730 people per 100,000 are affected with uveitis worldwide. Approximately 20% of patients develop ocular hypertension and many of these progress to glaucomatous optic nerve damage [111].

5.2 Pathogenesis

An equilibrium between aqueous production and drainage maintains a normal IOP, which is distorted in patients with uveitis [112]. Inflammation in the eye leads to the breakdown of the blood-aqueous barrier, thereby releasing inflammatory cells, proteins, debris, or fibrin in the eye causing mechanical obstruction of trabecular meshwork and alteration of aqueous composition thus, increasing resistance to outflow. Glaucoma can present in an open-angle stage or a closed-angle stage [113, 114].

5.3 Physiological changes in aqueous composition in uveitis

Intraocular inflammation leads to increased vascular permeability which results in the release of inflammatory cells, proteins, prostaglandins, and cytokines into the aqueous [112, 115]. The inflammatory cells narrow the trabecular pores resulting in dysfunction and swelling of trabecular lamellae and endothelial cells, hence disrupting aqueous outflow [116]. Prostaglandins contribute to elevated IOP by increasing the aqueous viscosity and are known to cause aqueous hypersecretion via PGE_1 and PGE_2 [117]. Cytokines stimulate neovascularisation and have a direct influence on aqueous humor dynamics [112]. The elevated protein content can result in aqueous sludging, causing compromise of aqueous outflow [118].

5.4 Anatomical changes seen at outflow facility

The cellular and biochemical changes result in morphological alteration at the level of the trabecular meshwork. On gonioscopic evaluation, uveitic glaucoma can be classified as a closed or open-angle stage. Open-angle stage is more frequently encountered [119, 120]. Increased vascular permeability and disrupted blood-aqueous barrier lead to infiltration of TM with inflammatory cells and proteins, which results in mechanical blockage and swelling of trabecular lamellae and endothelial cells. This eventually causes scarring and damage to the TM [121].

Intraocular inflammation leads to adhesions of pupillary margins with the anterior lens capsule forming posterior synechiae. It leads to pupillary block if they extend 360 degrees, obstructing the passage of aqueous humor into the anterior chamber and hence forming iris bombe and causing angle closure glaucoma. Another mechanism of the pupillary block is caused by occlusio pupillae, where the inflammatory cells and

protein form a fibrin membrane covering the pupillary margin and adhering to the anterior lens capsule, hence causing occlusion of the transfer of aqueous humor into the anterior chamber. Iris bombe formation eventually leads to the formation of PAS, thereby, closing the angle structures. Neovascularisation induced by cytokines may be witnessed at the angle in chronic uveitis, which pulls the iris and causes angle closure. Inflammation and swelling of the ciliary body lead to its forward rotation and hence causing non-pupillary block angle closure [122, 123].

5.5 Ocular conditions associated with inflammatory glaucoma

Uveitic glaucoma can be due to idiopathic ocular conditions, infective causes or systemic causes. With the advent of antimicrobial therapy, there is a drastic reduction in uveitic glaucoma due to infective pathology. The mechanism and progression of glaucoma depend on the etiology of uveitis and has been reported as more common in Fuchs heterochromic uveitis, Posner-Schlossman syndrome, herpetic uveitis, and Juvenile idiopathic arthritis (JIA) [124–128].

Ocular conditions:

- Fuch's Heterochromic Iridocyclitis
- Posner-Schlossman Syndrome
- Sympathetic ophthalmitis

Infective conditions:

- Viral (Herpes simplex, zoster, CMV)
- Syphilis
- Hansen disease

Systemic conditions:

- Juvenile Idiopathic Rheumatoid Arthritis
- Tuberculosis
- Sarcoidosis
- Behcet's

5.6 Signs and symptoms

The patient may present with symptoms of blurred vision, ocular pain, redness, brow ache, redness, and other ocular disturbances like photophobia and colored halos due to corneal edema in patients with markedly elevated IOP. The corneal examination may show band-shaped keratopathy, healed herpetic scars, and keratic precipitates on the endothelium. The anterior segment may reveal iris nodule, neovascularization, heterochromia, iris atrophy, posterior synechiae, and peripheral

anterior synechiae. The lens may reveal pigment on the anterior lens capsule and development/ progression of cataracts. Gonioscopy may show the presence of PAS and the degree of angle closure. May show features of fine vascularization in the trabecular meshwork, occasional trabecular precipitates, hypopyon, hyphaema, or fibrin deposition. Optic nerve evaluation and visual field assessment for glaucomatous damage must be done and recorded. Other possible posterior segment findings may include cystoid macular edema, retinitis, perivascular sheathing, choroidal infiltrates, or retinal detachment.

5.7 Management of uveitic glaucoma

The treatment approach in a case of uveitic glaucoma depends on various factors, but most importantly on a careful diagnosis of underlying etiology, strict control of inflammation and IOP, and constant monitoring for early glaucomatous damage and progression to initiate appropriate management. A rheumatologist's opinion to control systemic disease is a must. The main aim of the therapy is providing symptomatic relief, preventing glaucomatous damage, reducing the recurrence of uveitis, preventing the formation of synechiae or neovascularization, and reducing the need for surgical intervention.

5.8 Medical management

The control of uveitis is necessary to minimize any further complications that occur due to uveitis. An immediate and aggressive anti-inflammatory therapy prevents IOP rise and adverse events of uveitis [129].

5.8.1 Corticosteroids

Corticosteroids are the first line of treatment for addressing non-infectious ocular inflammation. The mechanism of action is by inhibiting the release of arachidonic acid and subsequent production of prostaglandins, thus reducing inflammation. It can be administered through various routes like topically, peri ocularly, intravitreally, and systemically depending on the severity of inflammation. Anterior segment inflammation is addressed by the use of localized drug delivery, which reduces systemic side effects [130–132]. Posterior segment inflammation can be addressed by periocular, intravitreal, or systemic application of steroids [133].

Immunosuppressive drugs: These drugs are generally reserved for refractory cases or when systemic side effects of chronic uses of corticosteroids are suspected. Most immunosuppressive agents take a minimum of 6 weeks to achieve maximum efficacy, so should be used in conjunction with corticosteroids in the beginning. It includes the use of drugs such as methotrexate, azathioprine, cyclosporine, tacrolimus, and other immunosuppressive agents [134–138].

Immunomodulatory agents: These biological agents are monoclonal antibodies, which are used as third-line drugs in recent times [139]. Favorable results have been seen with the usage of biological modulators, especially Adalimumab in the treatment of treating JIA-associated and pediatric refractory panuveitis [140].

Anti-inflammatory treatment must be given in association with topical cycloplegic drugs in acute uveitic episodes. Topical cycloplegics (atropine 1%, homatropine 1%, tropicamide 1%, cyclopentolate 1%) are used to relieve ciliary spasms, break acutely formed posterior synechiae, or prevent them from forming if started early in the disease

process [141]. Treatment of specific etiologies such as herpes simplex or varicella-zoster requires prescription of antiviral therapy along with antiglaucoma medications [142].

5.8.2 Antiglaucoma treatment

Traditionally, beta blockers and CAI have been used as a first-line therapy to control IOP spikes in uveitic glaucoma patients. Beta-blockers are considered the drug of choice to lower the IOP elevation in patients of uveitic glaucoma by reducing aqueous humor production [143, 144]. CAIs are frequently used as 1st line management along with beta-blockers in uveitic glaucoma [142] or in cases where beta blockers are contraindicated. CAIs lead to the alteration of the ion transport mechanism in the ciliary epithelium thereby, reducing the production of aqueous humor [144]. Brimonidine is an Alpha-2 adrenergic agonist which leads to the reduction of IOP via a dual mechanism. They reduce aqueous production at ciliary epithelium and also enhance uveoscleral outflow [145, 146] and their mydriatic effect is useful in preventing posterior synechiae formation in uveitic eyes [110]. The role of PGA in the management of uveitic glaucoma is controversial because of the high risk of inducing anterior uveitis, blood-aqueous barrier disruption, cystoid macular edema, and reactivation of Herpes simplex keratitis [110]. Ripasudil, a Rho-associated protein kinase inhibitor shown to lower IOP by altering trabecular meshwork, has been approved in Japan in 2014. It has been effective in lowering IOP in approximately 50% of eyes of UG [147]. Hyperosmotic agents like glycerol and mannitol are used in acute elevation of IOP.

Laser therapy: Laser peripheral iridotomy (LPI) must be performed for eyes that have a narrow anterior chamber angle susceptible to a primary acute angle closure attack [148]. An ideal peripheral iridotomy of 300– 350 microns is required to prevent acute angle-closure glaucoma [149].

5.8.3 Surgical management

Clinically about 30% of uveitic eyes do not respond to maximal medical therapy and require surgical intervention [150]. Inflammation-induced accelerated scarring is a challenging problem as it is associated with a higher risk of surgical failure. Adequate control of inflammation, both pre-operative and post-operative, and IOP control are desirable prior to surgical intervention for better results [151]. A quiescent phase of a minimum 3 months is considered ideal, which can be attained by the use of corticosteroid therapy. The risk of post-operative hypotony is more in uveitic glaucoma cases as chronic and relapsing intraocular inflammation leads to ciliary body impairment. Both trabeculectomy (with and without adjunctive antifibroblast medications) and aqueous drainage implants are used to control IOP [152]. Glaucoma drainage implants are preferred in patients with extensive conjunctival scarring, or after failed trabeculectomy [153–155]. The other significant risk factors for surgical failure are male sex, age younger than 45 years, and non-granulomatous uveitis [156].

Trabeculectomy is considered gold standard surgery for UG with uncontrolled IOP with maximal medical therapy and in cases of angle closure with extensive PAS formation. A bleb-dependent fistula is formed that helps aqueous drainage from the anterior chamber into subconjunctival space. Adequate control of IOP (< 21 mm Hg) has been seen in various studies in patients with uveitis who underwent trabeculectomy [157–159]. Studies have reported failure of the procedure in patients with significant post-op inflammation [157].

The results of unaugmented trabeculectomy are variable and are particularly poor in young patients with UG [160], as a result of an accelerated wound-healing response. Trabeculectomy augmented with MMC or 5-FU has shown good surgical success rates in patients with a high risk of failure, due to its effect of minimizing scarring of the filtering bleb [161].

Glaucoma Drainage Devices: Glaucoma drainage implants have been used increasingly in the treatment of uveitic glaucoma. They are especially useful in cases with unhealthy conjunctiva as primary surgery or after failed trabeculectomy surgery. Drainage devices may be valved (AGV), or non-valved (Baerveldt glaucoma implant, BGI, and Molteno implant). A study has reported AGV to have success rates of up to 94% at 4 years follow-up in chronic UG [162]. The AGV is considered effective in reducing IOP, decreasing the number of glaucoma medications, and preserving vision [162].

Cyclophotocoagulation: Laser cytophotocoagulation is used to destroy the ciliary body where aqueous humor is produced. Unfortunately, it leads to the aggravation of intraocular inflammation, and is reserved as the last step for eyes with uncontrolled IOP and poor visual potential [158].

5.9 Conclusion

Strict control of Inflammation and finding the root cause that triggers inflammation is one of the first steps in controlling the adversaries caused by Uveitis. With the advent of more aggressive and comprehensive medical control of uveitis, the prognosis for UG patients has drastically changed compared to a few years ago. Management is directed at the diagnosis of the underlying condition and appropriate management of the local or systemic disease for adequate control of inflammation and deferring repeated attacks. Better medical and surgical options are available for patients suffering from UG. Apart from traditional trabeculectomy, various implantable drainage devices are available, which have proven to be effective and successful. Long-term large prospective studies are warranted for a better understanding of long-term efficacy. Non-penetrating Goniotomy procedures appear to be a lucrative option in pediatric patients and even adults. Other glaucoma surgical options like minimally invasive glaucoma surgery (MIGS) may also be effective in these patients, but those approaches are still under evaluation. A booming role of stem cell therapy has shown effectiveness in the management of various diseases, but its role is yet to be discovered in patients with uveitic glaucoma.

6. Neovascular glaucoma

6.1 Introduction

Neovascular glaucoma (NVG) is a sight-threatening condition, especially in developing countries. NVG occurs secondary to several diseases that affect the eye, the most common being proliferative diabetic retinopathy (PDR) [163], ischemic retinal vein occlusion [164]' and less frequently CRAO and ocular ischemic syndrome (OIS). It is a significant cause of visual morbidity due to its aggressive nature and resistance to the currently available medical therapy, especially in the latter stages of the disease. Only 3% of cases of NVG are caused by inflammation without retinal ischemia [165].

The central mechanism is a hypoxic posterior segment, leading to increased vascular endothelial growth factor (VEGF) formation. VEGF, an endothelial cell mitogen

is synthesized by several types of retinal cells, but under ischemic conditions, Muller cells are the primary source.

The cytokine-rich environment promotes the formation of fibrovascular tissue that gradually covers the trabecular meshwork causing impairment of AH outflow and a resultant increase in IOP [166]. In the initial stages, the angles remain open, but the myofibroblasts' proliferation eventually creates a synechial angle-closure [167] and further IOP elevation. Many other substances that might be involved in angiogenesis are under investigation. These include insulin-like growth factors I and II [168], insulin-like growth factors binding proteins 2 and 3 [169], basic fibroblast growth factors [170], platelet-derived growth factors [169], and interleukin 6 [169].

1. Clinical manifestations

Although there is a certain degree of overlap, it is convenient to divide the stages of NVG into the following:

1. Stage of Rubeosis iridis

2. Stage of Secondary open-angle glaucoma

3. Stage of Secondary synechial angle-closure glaucoma

2. Early stage (Rubeosis Iridis)

The first visible sign of incipient NVG is tiny tufts of new vessels at the pupillary margin which may at times appear just as tiny red dots. One should maintain a high index of suspicion and carefully examine under high magnification at the slit lamp. These small vessels can be easily overlooked, especially in darkly pigmented irises if casually viewed. In case a contact gonioscopy is used at the initial examination, the light pressure on the lens is sufficient to collapse these neovascular tufts and render them clinically invisible. Similarly, these vessels will be missed if a dilated examination is done. The new vessels will continue to grow radially over the surface of the iris in an irregular meandering manner toward the angle, sometimes joining dilated blood vessels at the collarette. At this stage, the IOP is usually normal and the new vessels may regress with the treatment of the primary pathology or may progress to involve the angle. At times, neovascularization of the angle (NVA) can occur with or without neovascularization of the iris (NVI), so a careful gonioscopy is a must in all eyes at high-risk for NVG, even in the absence of pupillary and iris involvement. NVI tends to begin where the greatest aqueous-tissue contact occurs, so, it is important to examine the other passageways for aqueous to enter the AC bypassing the pupil, for example, a peripheral iridotomy.

All patients diagnosed with severe NPDR should also be examined for early NVI as the presence of NVI may direct the clinician to look for CNP areas in the retina with an FFA.

3. Stage of secondary open-angle glaucoma

If the process of rubeosis continues, the new vessels continue to grow across the iris surface and join the circumferential ciliary body artery. On reaching the angle, the new vessels cross the ciliary body band and scleral spur onto the TM. Until a significant portion of the TM is covered by NVA, the IOP may be completely normal. A fibrovascular membrane, which is invisible on gonioscopy, commonly accompanies NVA and may block enough of the TM and raise the IOP thus causing a secondary form of open-angle glaucoma. Pathological NVA is differentiated from normal NVA

by the former crossing the scleral spur (diagnostic) and the latter as a visible circumferential blood vessel over the peripheral iris seen during gonioscopy.

4. Stage of secondary synechial angle-closure glaucoma

If the second stage continues the fibrovascular membrane contract producing peripheral anterior synechiae (PAS). As these PAS coalesce, synechial angle closure occurs and the IOP may remain continuously elevated.

6.2 Clinical features

The prototypic picture of NVG is quite characteristic. In the stage of rubeosis iridis, a careful examination would reveal the new vessels at the pupillary area with normal IOP. The second stage of open-angle of NVG would have NVI/ NVA with or without elevated IOP. As the third stage of angle closure ensues, the IOP is usually elevated. The vision may be severely reduced due to an edematous cornea and the primary disorder underlying the NVG. There is congestion of the globe with marked pain. The IOP can be very high (>40 mm Hg or higher), but in some cases, such as carotid artery obstructive disease, it may be normal or even subnormal. However, if the patient is young and the endothelium is healthy, the cornea may remain clear with a high IOP. In case of very elevated IOP with corneal edema, the NVI/NVA may be missed thus causing a diagnostic dilemma. So, a repeat slit-lamp examination is very important to note the NVI/NVA when the cornea clears on treatment. There can be associated aqueous flare due to leakage of proteins from the new iris vessels and seen only when the cornea clears. There can be a distortion of the pupil and ectropion uvea due to the radial contraction of fibrovascular tissue during the late changes. Gonioscopy may show synechial angle closure at different levels with NVA. At the burnt-out stage, the picture of a smooth zippered-up line of iridocorneal adhesion is pathognomonic, at which stage NVA may be absent but other signs like ectropion uvea and the fundus pathology should help in making the diagnosis.

6.3 Role of fluorescein angiography

Iris fluorescein angiography (FA) demonstrates leakage from damaged iris vessels long before new vessels can be detected on slit-lamp examination. This is due to the production of VEGF, which is also a potent Vaso permeability factor and is likely to be 50,000 times more potent than histamine [170]. The fluorescein leakage occurs throughout the iris which persists and increases with time, unlike in the benign forms of capillary incompetence (e.g. pseudoexfoliation). In one study, NVI could be detected in 37% of eyes before the development of clinically visible new vessels [171].

Grading of Iris Neovascularization [172] – as proposed by Teich and Walsh

Grade 0- No iris neovascularisation

Grade 1- Less than 2 quadrants of NV at iris pupillary zone

Grade 2- More than 2 quadrants of NV at iris pupillary zone

Grade 3- Grade 2 + less than 3 quadrants of NV at iris ciliary zone and/or ectropion uveae

Grade 4- More than 3 quadrants of NV at ciliary zone and/or ectropion uveae

NVA grading [173] is as follows:

Grade 1 - Fine neovascular twigs cross scleral spur and ramify on the trabecular meshwork, involving ≤2 quadrants;

Grade 2 - Neovascular twigs cross scleral spur and ramify on the trabecular meshwork, involving ≥2 quadrants;

Grade 3 - In addition to the trabecular meshwork, PAS involving 1 to 3 quadrants;
Grade 4 - PAS involving ≥3 quadrants.

6.4 Management

The management of NVG involves decreasing the primary ischemic drive by either pan-retinal photocoagulation (PRP) and/or anti-angiogenic injection and control of IOP by ocular hypotensive therapy [167]. In the early open-angle glaucoma stage, AGMs or PRP may be effective. However, an overwhelmingly great number of patients do not respond to medical treatment in the closed-angle stage. The exact reason is not known but presumably, the high IOP inhibits the drug to penetrate the cornea in the presence of corneal epithelial edema and the ischemic status further prevents the absorption of the drug from the AH to the ciliary circulation. Surgical options include trabeculectomy, and GDD in eyes with vision potential while cyclodestructive procedures are reserved when the former is not feasible or in absolute eyes. Both trabeculectomy and GDD act by creating alternative channels for AH drainage and thus reducing the IOP whereas cyclodestructive techniques are based on partial destruction of the ciliary body which decreases AH production, and therefore lowers the IOP.

6.4.1 Medical management

Management of NVG mainly targets treatment of the underlying disease process responsible for rubeosis and treatment of the increased IOP.

6.4.2 Treatment of the primary pathology

A. Pan retinal photocoagulation (PRP)
A.1. Early-stage therapy
During the stage of early NVI (Rubeosis iridis), the mainstay in therapy is pan-retinal photocoagulation (PRP). The most widely accepted mechanism by which PRP works is by destroying the retinal outer layer and thereby decreasing oxygen demand since the outer photoreceptor-retinal pigment epithelium complex accounts for the majority of total retinal oxygen consumption. This allows choroidal oxygen to diffuse into the inner retina, decreasing not only inner retinal hypoxia but also reducing the stimulus for the release of angiogenic factors. There is sufficient documentation that PRP decreases ocular VEGF levels and subsequent regression of the NVI in CRVO [174] and PDR [175].
It has been noted that treatment with approximately 1,200–1,600 spots is required to cause regression of NVI. Ohnishi and colleagues [176] documented regression of rubeosis in 68% of patients and normalization of IOP in 42% of patients treated with PRP. There is also a higher success rate for glaucoma filtering procedures when PRP is performed [176]. However, the results of PRP in CRAO are not as effective as in CRVO and PDR [177].
A.2. Late-stage therapy
In this stage usually, synechial angle closure has set in, and the management of glaucoma becomes increasingly difficult. In the presence of clear media, PRP should be performed as soon as possible to eliminate the stimulus for new vessel formation; otherwise, filtration surgery is more likely to fail. Regression of NVI can occur within

days to weeks of completed PRP. Filtration surgery should be done at least 1 week and preferably 3 to 4 weeks after completion of PRP.

A.3. Endophotocoagulation

Intraoperative PRP is useful in situations where routine PRP cannot be done due to hazy media. It is done in conjunction with intraocular surgery like cataract extraction or vitrectomy and can be just as effective as standard photocoagulation and hence extensively used, especially during vitrectomy [178].

B. Role of anti-VEGF agents

B.1. Intravitreal bevacizumab

In situations where PRP cannot be done due to associated ocular conditions such as poor pupillary dilatation, corneal edema, cataract, or vitreous hemorrhage, intravitreal Bevacizumab (IVB) has been shown to cause marked and rapid regression of anterior segment neovascularization in NVG. Marked regression of iris neovascularization has been noted in various case reports within a median of 8 days (range 1 to 10 days) [179]. Although the long-term effectivity is not known, even a transient effect could be of benefit in the preoperative preparation of filtering surgery for NVG." Bevacizumab is applied in the dose of 1.25 mg/0.05 ml intravitreally and 0.25 mg/0.02 ml intracamerally [180].

6.4.3 Treatment of elevated IOP

A. Medical therapy

In the secondary open-angle glaucoma stage, all the standard antiglaucoma medications will be effective to some degree in lowering the IOP. However, in all stages of NVG, one must avoid the usage of pro-inflammatory drugs like Prostaglandin analogs and Pilocarpine eye drops. With extensive synechial angle closure, medications that decrease aqueous production, such as topical β-blockers and carbonic anhydrase inhibitors, are beneficial but do not lower the IOP to a normal range in the face of a highly inflamed state of the eye. Frequently, oral acetazolamide may be required to control IOP. Intravenous mannitol at a dosage of 1mg/kg/body weight may temporarily reduce IOP but should be used judiciously in hypertensive patients. Oral glycerol may not be as effective as mannitol but can help to reduce IOP till a definitive filtration surgery can be planned. It is, however, contraindicated in diabetics. The two other medications that are of the greatest benefit clinically are topical atropine 1% three times per day to decrease ocular congestion, and topical steroids four times per day to decrease ocular inflammation [181].

B. Conventional surgery

B.1. Trabeculectomy

Filtration surgery in NVG should be reserved for eyes that have the potential for useful vision and when the extent of the PAS is >180°. It should be preferably performed when the eye is quiet; otherwise, intraoperative and postoperative hemorrhages are likely to occur. Also, the presence of active neovascularization may lead to late bleb failure through conjunctival scarring at the filtration site.

Higashide T [182] et al studied 61 eyes of 54 patients with NVG treated by trabeculectomy following intraocular bevacizumab injection. The surgical success rate at a mean follow-up of 45+ 22.2 months was 86.9 + 4.3%, 74.0 + 6.1%, and 51.3 + 8.6% at 1,3, and 5 years. Effects of adjunctive use of intraocular anti-VEGF agents on glaucoma filtration surgeries for NVG have been evaluated in several studies [183, 184]. Less post-operative hemorrhagic complications and better surgical outcomes were anticipated because of the remarkable rapid and steady suppression of

rubeosis after intraocular injection of bevacizumab. Indeed, postoperative hyphema was significantly less frequent when bevacizumab was used before trabeculectomy [185] or tube shunt surgery [186].

Risk factors for surgical failure of trabeculectomy in eyes with NVG were found to be younger age, previous pars plana vitrectomy (PPV), extensive peripheral anterior synechia, pseudophakia, and postoperative hyphema [187, 188].

B.2. Glaucoma drainage implants

When conventional surgery fails or is not possible because of excessive conjunctival scarring, insertion of a drainage device may be indicated. GDIs can be valved like the Ahmed Glaucoma valve and non-valved like the Baerveldt / Molteno and Aurolab aqueous drainage implant. Sevim et al. [189] assessed the efficacy of preoperative IVB injection before AGV implantation in NVG and found a better surgical success rate in the study group (79%) than in the control group (64%), with reduced early postoperative complications such as fibrinous reaction in the AC as well as hyphema. Shen et al. [188] found similar surgical outcomes in neovascular glaucoma patients who underwent trabeculectomy with MMC versus AGV implantation, with 20 patients in each group and an average follow-up of 31 months for the AGV group and 25 months for the trabeculectomy group. Success was 70% and 65% at 1 year and 60% and 55% at 2 years after AGV and trabeculectomy, respectively. Hyphema was the most common complication in both groups.

B.3. Ciliodestructive procedures

In end-stage NVG, when there is total synechial angle closure and no useful vision remaining, there is no indication for surgical intervention, and control of pain becomes the primary therapeutic aim. Ciliodestructive procedures were widely used before the advent of antifibrotic agents and anti-VEGF agents in the management of NVG. Although they may be highly effective in lowering IOP, the visual results are disappointing, especially with cyclocryotherapy (CCT). Sympathetic ophthalmia, RD, anterior segment ischemia, and phthisis have all been reported with cyclocryotherapy [190]. Direct laser cyclophotocoagulation seems to have better control and titration of the ciliary processes destroyed and a lower complication rate, but the percentage of patients with NVG who lose total vision remains high, with a long-term vision loss of 46.6% as reported by Shields and Shields [191]. Transscleral Cyclophotocoagulation (TSCPC) is another method. There is less elevation of IOP in the immediate postoperative period, along with less inflammation and pain than after CCT. With the contact system, there is a report of 140 eyes treated, 45 of which had NVG. An IOP of less than 19 mm Hg was achieved in 40% of the eyes with NVG. It was also noted that 50% of the serious complications were in eyes with NVG, including one eye with phthisis and one with traction RD [192].

In the meta-analysis of the surgical management of NVG by Shchomak et al [193]

there was no statistically significant difference in IOP-lowering capacity between the GDDs vs cyclophotocoagulation group. However, failure rates and proportion of patients with loss of LP were favorable to the GDDs group.

6.4.4 Conclusion

Neovascular glaucoma remains a therapeutic challenge. Despite many advances in the treatment of NVG, the visual prognosis remains poor. Early detection of neovascularization and prophylactic treatment with PRP directed at the ischemic retina are key elements in preventing a visually devastating outcome of this disease. Once IOP becomes elevated, successful management of the disease may be extremely

difficult. Although the ideal surgical management of the neovascular glaucoma procedure has yet to be determined, trabeculectomy with antimetabolite therapy, aqueous shunt implants, and diode laser cyclophotocoagulation is the best surgical options. Current research on ocular angiogenesis and the advent of new pharmacological agents with activity against vascular endothelial growth factors have increased our treatment options for combating this serious disease. Bevacizumab may be a valuable addition to the treatment of NVG by hastening the resolution of anterior segment neovascularization and thereby improving the results of glaucoma surgeries.

Abbreviation list

PK	penetrating keratoplasty
IOP	intraocular pressure
PPKG	post penetrating keratoplasty glaucoma
PAS	peripheral anterior synechiae
TM	trabecular meshwork's
AC	anterior chamber
DCT	dynamic contour tonometer
GAT	Goldmann applanation tonometry
ORA	ocular response analyzer
UBM	ultrasound biomicroscopy
IOL	intraocular lens
CAI	carbonic anhydrase inhibitors
MMC	mitomycin C
5-FU	5-fluorouracil
GDD	glaucoma drainage device
SLT	selective laser trabeculoplasty
ALT	argon laser trabeculoplasty
GDIs	glaucoma drainage implants
LIG	lens induced glaucoma
PAG	phacoanaphylactic glaucoma
PLG	phacolytic glaucoma
LPIG	lens-particle induced glaucoma
PMG	phacomorphic glaucoma
PGA	prostaglandin analogues
AGM	anti-glaucoma medications
LPI	laser peripheral iridotomy
IgG	immunoglobulin G
AGV	Ahmed glaucoma valve
BGI	Baerveldt glaucoma implant
PGE_1	prostraglandin E_1
PGE_2	prostraglandin E_2
JIA	juvenile idiopathic arthritis
CMV	Cytomegalo virus
UG	uveitic glacucoma
MIGS	minimally invasive glaucoma surgery
NVG	neovascular glaucoma
PDR	proliferative diabetic retinopathy
CRAO	central retinal artery occlusion
CRVO	central retinal vein occlusion

OIS	ocular ischemic syndrome
VEGF	vascular endothelial growth factor
NVA	neovascularization of the angle
NVI	neovascularization of the iris
FA	fluorescein angiography
PRP	pan-retinal photocoagulation
IVB	intravitreal bevacizumab
PPV	pars plana vitrectomy
CCT	cyclocryotherapy
RD	retinal detachment
TSCPC	transscleral cyclophotocoagulation

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