Glaucoma risks in advanced corneal surgery

Vincenzo Maurino*,1, Francesco Aiello*,†
*Moorfields Eye Hospital, NHS Foundation Trust, London, UK
†Department of Experimental Medicine and Surgery, University of Rome Tor Vergata, Rome, Italy
†Corresponding author: Tel.: +44-207566-2045; Fax: +44-207566-2019, e-mail address: vincenzo.maurino@moorfields.nhs.uk

Abstract
Penetrating corneal transplant (PKP) surgery has been performed for centuries as the procedure of choice to restore vision in cases of advanced corneal disease. However, the last two decades have seen the introduction of lamellar corneal surgery (deep anterior lamellar keratoplasty, DALK; Descemet stripping-automated endothelial keratoplasty, DSAEK; and Descemet membrane endothelial keratoplasty, DMEK) which has shown several advantages over PKP and has rapidly gained popularity, given its benefits.

Glaucoma after corneal graft surgery is an important cause of visual loss and graft failure. The main risk factors for developing glaucoma after any type of corneal graft are steroid-related intraocular hypertension and pre-existing glaucoma. The incidence of glaucoma after corneal graft surgery varies according to the specific risk factors and the type of corneal graft performed. One major advantage of modern layer selective lamellar keratoplasty is the reduced risk of glaucoma compared with PKP. This reduced glaucoma risk after corneal lamellar graft surgery is mainly due to the less destructive surgical nature of the lamellar procedures and also the reduced use of postoperative steroid treatment.

Glaucoma can complicate not only corneal transplantation but has also been observed following other anterior segment procedures from laser refractive surgery to keratoprosthesis.

The aim of this chapter is to describe the incidence, etiology, and management of glaucoma after corneal transplant and some common corneal surgical procedures.

Keywords
Glaucoma, Penetrating keratoplasty, Endothelial keratoplasty, Anterior lamellar keratoplasty, Steroid-induced glaucoma, Urrets-Zavalia syndrome
Corneal transplant surgery has witnessed enormous improvements in techniques and technologies especially over the last two decades allowing the switch from full-thickness corneal transplant surgery (penetrating keratoplasty (PKP)) to lamellar selective keratoplasties.

The first reported full-thickness corneal transplant was performed by Eduard Zirm in 1905 (Zirm, 1906). He carried out a 5-mm PKP in a patient with a chemical corneal injury. Subsequently, in the mid-1900s, Charles Tillett performed the first layer selective posterior corneal lamellar graft (Tillett, 1956). Despite the obvious limitation of the surgical technique used at the time, 1 year postsurgery the posterior corneal graft remained attached with a clear cornea; however, the patient did develop severe postoperative glaucoma. Since these first attempts, there have been many developments in corneal graft surgery but the major benefit was the introduction of antirejection steroid drugs treatment. Topical steroid treatment is now established to be the mainstay for the prophylaxis and treatment of corneal graft rejection, improving outcomes, and graft survival (Nguyen et al., 2007; Ross et al., 2009). However, the hypertensive side effects of steroids drugs, increased intraocular pressure (IOP), and therefore glaucoma (Price et al., 2014) are well known.

In the last two decades, PKP has evolved into the more refined layer selective corneal transplant surgery.

Deep anterior lamellar keratoplasty (DALK) has replaced PKP for disorders affecting the corneal stroma but sparing the endothelium thus eliminating the risks of endothelial graft rejection and reducing subsequent risk of graft failure.

Endothelial keratoplasty (EK) selectively replaces the corneal endothelium in patients with endothelial disease alone. The first attempt of modern EK surgery was described by Melles et al. (1999a) and termed deep lamellar endothelial keratoplasty (DLEK). It involved a complex resection of the posterior donor corneal stroma and its replacement with a new resected donor posterior layer through a very large corneal incision. This technique has now been abandoned because of poor visual results and severe complications. Later, Melles et al. (2004) described an evolution of DLEK where the recipient Descemet instead of being dissected is “stripped” with the “descemetorhexis” technique leading to Descemet stripped endothelial keratoplasty. The term Descemet stripping-automated endothelial keratoplasty (DSAEK) was introduced by Mark Gorovoy who first reported the use of a microkeratome for donor tissue dissection (Gorovoy, 2006). The latest evolution of EK is represented by Descemet membrane endothelial keratoplasty (DMEK) in which not only the recipient but also the donor endothelium is manually stripped avoiding any donor stroma tissue thus leading to faster visual recovery and less risk of graft rejection (Guerra et al., 2011b; Price et al., 2009b).

The new lamellar selective corneal graft technique has excellent postoperative results (Cheng et al., 2013; Keane et al., 2014; Price and Price, 2013; Price et al., 2013; Sogutlu Sari et al., 2013) along with reduced risk of sight-threatening glaucoma compared with PKP (Haddadin and Chodosh, 2014).

Despite these technical improvements, glaucoma disease can still occur after any kind of keratoplasty procedure. To date, the main cause of glaucoma in grafted patients is the long-term steroid treatment that is needed to prevent graft rejection and failure.
1 MECHANISM OF STEROID-INDUCED GLAUCOMA

In susceptible individuals, prolonged or intensive steroid therapy can produce ocular hypertension (OHT), which over time can cause secondary glaucoma with optic nerve damage and ultimately visual loss if the steroid treatment is not discontinued timely (Goldmann, 1962). Steroid-induced glaucoma has the same features of primary open-angle glaucoma with its typical characteristics of open iridocorneal angle and a reduction of trabecular meshwork outflow (Armaly, 1965). Patients with a pre-existing diagnosis of glaucoma can also experience an increase of IOP when using steroid medication, despite previously well-controlled IOP (Becker and Hahn, 1964; Kiddee et al., 2013). It has been reported that when treated with topical steroids for 4–6 weeks, 30% of the population would show a rise in IOP of 6–15 mmHg and 5% of the population an increase over 16 mmHg (Becker, 1965).

The pathogenic mechanism in which steroids induce OHT is not yet fully understood and different theories have been proposed. An alteration in the outflow with trabecular meshwork dysfunction is thought by most to be a key factor.

The trabecular meshwork is composed of three layers: the uveal part adjacent to the anterior chamber, the corneo-scleral meshwork, and the juxtacanalicular meshwork which forms the inner wall of Schlemm’s canal and is thought to be the major site of outflow resistance (Hann et al., 2014). The trabecular meshwork works as a one-way drainage valve that permits aqueous to leave the eye by bulk flow, but limits flow in the opposite direction. Theoretically, obstruction of the trabecular meshwork will lead to an increase in IOP.

Different theories of trabecular meshwork dysfunction under the effect of steroids have been proposed and subsequently summarized recently by Kiddee et al. (2013).

1. Increase in extracellular deposits in the trabecular meshwork.

   Steroids may alter protein synthesis and inhibit extracellular matrix degradation. This can lead to an aggregation of the extracellular matrix and a subsequent decrease in aqueous outflow (Kersey and Broadway, 2006).

2. Inhibition of trabecular meshwork cell function, in terms of:
   (a) inhibition of the active phagocytosis process with a decrease in debris and pigment material removal (Zhang et al., 2007),
   (b) stabilization of lysosomes resulting in an accumulation of hydrophilic mucopolysaccharides

   Both of the above can lead to a more crowded trabecular meshwork (Wilson et al., 1993).

3. Alteration of the trabecular meshwork cytoskeleton.
   – Corticosteroid drugs can alter the trabecular meshwork cytoskeleton function in terms of regulating aqueous outflow, causing a progressive reorganization of the microfilaments. This process seems to be reversible if steroid use is discontinued (Clark et al., 1994).
4. Increase in cell adhesion molecules.
   – Increase in the number of the tight junction and zonula occludens proteins at
     the level of trabecular meshwork, with a subsequent reduction in aqueous
     drainage (Underwood et al., 1999).

Furthermore, recent findings highlighted that use of topical steroids can induce OHT
through an upregulation of myocilin gene responsible of IOP increase (Polansky
et al., 1997; Stone et al., 1997).

While IOP increase can occur after administering steroids by various routes, it
is most commonly a complication of topical corticosteroid application. It has been
found that the higher the steroid potency, the greater the ocular hypertensive effect
(Cantrill et al., 1975). Typically, in responsive patients, the IOP rises after weeks of
continual corticosteroid therapy in both normal (Armaly, 1963) and glaucomatous
eyes (Cantrill et al., 1975). Generally, after the steroid treatment has been discon-
tinued the IOP returns to normal values within 1–4 weeks; the rarer acute response
may resolve within a few days of steroid cessation (Weinreb et al., 1985). Type
I diabetes mellitus (Becker, 1971), high myopia (Podos et al., 1966), certain
connective tissue diseases (Gaston et al., 1983), and a positive family history of
open-angle glaucoma (Becker, 1965) are risk factors for a steroid-induced
increase in IOP.

## 2 LAMELLAR AND PENETRATING KERATOPLASTY

The use of topical steroids remains the main treatment after corneal transplant
surgery to prevent and treat graft rejection, which is the principle cause of trans-
plant failure (Price et al., 2009a). Standard corneal graft immunosuppression treat-
ment regimen is based on topical corticosteroid, administrated at least four
times per day for the first month followed by a tapering dose for 1-year post-
PKP transplant (Price et al., 2009a). If a rejection episode occurs, then the steroid
administration is usually increased to revert the rejection and avoid a consequent
graft failure.

The Australian Corneal Graft Registry (ACGR) showed a 1-year graft survival
rate following PKP (keratoconus indication was 32%), of 87% that dropped to
46% at 15 years (Williams et al., 2008). This is primarily due to continuous loss
of donor endothelial cells leading to graft failure (24%) and irreversible rejection
(34%) (Tan et al., 2009).

Contrariwise, DALK spares the host endothelium minimizing the risk of endo-
thelial cell loss and subsequent endothelial rejection. Several studies have shown that
one of the major advantages of DALK compared with PKP is the reduced long-term
rejection rate (Sogutlu Sari et al., 2013; Tan et al., 2012). This translates in a signif-
icient reduced need for steroids use after DALK compared with PKP, ultimately
thereby reducing the risk of developing post-graft glaucoma (Al-Mahmood et al.,
2012; Al-Mohaiemeed et al., 2007).
In a retrospective comparative study between DALK and PKP for keratoconus, Watson et al. (2004) recorded a graft rejection episode in 28% of cases in PKP group versus 7% in DALK group in a mean follow-up of 28 months. Han et al. (2009) when comparing DALK versus PKP surgery for keratoconus found similar results with 16% of eyes in PKP group experiencing a graft rejection episode compared with 0% in DALK group. However, DALK does have a steeper learning curve compared with PKP and the possibility of suboptimal visual outcomes due to interface-related problems, mainly in cases of manual pre-Descemetic dissection.

Like DALK has several advantages over PKP and it is the preferred technique for patients with healthy corneal endothelium, EK is now considered the best surgical treatment for corneal endothelial disease alone. EK surgery is performed through a small incision similar to cataract surgery. Therefore, the problems of open sky surgery (PKP) are almost fully eliminated (expulsive hemorrhage, sutures-related complications, wound dehiscence, and long-term weakening of the eyeball). EK allows rapid visual recovery and minimal refractive change compared with conventional full-thickness PKP (Price and Price, 2010; Table 1).

Similar to DALK, EK compared with PKP has a lower risk of immunologic rejection. DSAEK was shown in a prospective, multicenter interventional study, to

Table 1 Differences in corneal keratoplasty technique

<table>
<thead>
<tr>
<th>Graft technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKP</td>
<td>• No stroma interface</td>
<td>• High postoperative astigmatism</td>
</tr>
<tr>
<td></td>
<td>• Suitable in full-thickness corneal perforation</td>
<td>• Open-sky surgery-related risks</td>
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<tr>
<td></td>
<td>• Faster learning curve</td>
<td>• Intensive postoperative steroid treatment</td>
</tr>
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<td></td>
<td>• Less expensive procedure</td>
<td>• Progressive postoperative endothelial cell loss</td>
</tr>
<tr>
<td></td>
<td>• Can be used for any indication</td>
<td>• Glaucoma exacerbation up to 53% reported</td>
</tr>
<tr>
<td></td>
<td>• Extra-ocular procedure/ more tectonical stability</td>
<td>• Wound dehiscence possible many years after procedure</td>
</tr>
<tr>
<td></td>
<td>• Spares the healthy endothelium layer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Less topical steroid use compared with PKP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Less rejection risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Early suture removal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No risk of endothelium rejection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Less risk of postoperative glaucoma</td>
<td></td>
</tr>
<tr>
<td>DALK</td>
<td>• Postoperative astigmatism similar to PKP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Stroma interface can reduce postoperative visual outcome (more in pre-Descemetic technique)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Not applicable in full-thickness perforation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Steep learning curve</td>
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Continued
have a graft survival rate of 94% (111 eyes) at 3-year follow-up with a reported rejection rate of 6.4% (Price et al., 2013). DMEK (where only the Descemet membrane single layer is transplanted) has a reported rejection rate of 1% or less in the first 2 years of follow-up (Price et al., 2014). EK does have a lower risk of glaucoma than PKP and also the lesser disruption of the ocular surface with EK make postoperative IOPs measurement significant easier and reliable compared with PKP (Daoud et al., 2013; Maier et al., 2014; Moisseiev et al., 2013; Vajaranant et al., 2008).

In conclusion, lamellar advanced corneal surgery main advantage is the reduced rejection and failure risk (Anshu et al., 2012b; Dapena et al., 2011) compared with PKP. As a direct consequence of the lesser rejection risk, the use of steroids after lamellar surgery can be reduced compared PKP, thereby decreasing the risk of developing postoperative steroid-related glaucoma (Table 2).

Table 1 Differences in corneal keratoplasty technique—cont’d

<table>
<thead>
<tr>
<th>Graft technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| EK              | • Postoperative astigmatism insignificant  
|                 | • More tectonical stability  
|                 | • Spares the healthy stroma  
|                 | • Less topical steroid use compared with PKP  
|                 | • Less rejection risk  
|                 | • Less risk of postoperative glaucoma | • Steep learning curve (more for DMEK technique)  
|                 |                                        | • Stroma interface can reduce postoperative visual outcome (more for DSAEK technique) |

PKP, penetrating keratoplasty; DALK, deep anterior lamellar keratoplasty; EK, endothelial keratoplasty; DSAEK, Descemet stripping-automated endothelial keratoplasty; DMEK, Descemet membrane endothelial keratoplasty.

Table 2 Glaucoma risk in corneal graft

<table>
<thead>
<tr>
<th>Glaucoma</th>
<th>PKP</th>
<th>DALK</th>
<th>EK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported risk</td>
<td>10–53%</td>
<td>0–17%</td>
<td>0–44%</td>
</tr>
<tr>
<td>Most important risk factor</td>
<td>Pre-existing glaucoma</td>
<td>Pre-existing glaucoma</td>
<td>Pre-existing glaucoma</td>
</tr>
<tr>
<td>Short-term causes</td>
<td>Iridocorneal angle distortion</td>
<td>Air left in the AC and pupillary block</td>
<td>Air left in the AC and pupillary block</td>
</tr>
<tr>
<td></td>
<td>OVD left the AC</td>
<td>OVD left in the AC</td>
<td>OVD left in the AC</td>
</tr>
<tr>
<td>Long-term causes</td>
<td>Steroid related Anterior synechiae</td>
<td>Steroid related</td>
<td>Steroid related</td>
</tr>
</tbody>
</table>

PKP, penetrating keratoplasty; DALK, deep anterior lamellar keratoplasty; EK, endothelial keratoplasty; AC, anterior chamber.
Irvine AR and Kaufman HE were the first to report an association between PKP and glaucoma (Irvine and Kaufman, 1969). Glaucoma has since been reported as an important and frequent cause of graft failure, and causes a higher risk of rejection (Huber et al., 2013).

Glaucoma after corneal transplant surgery is defined as the presence of persistent elevated IOP, above 22 mmHg (Haddadin and Chodosh, 2014; Huber et al., 2013) or an IOP rise >10 mmHg from the baseline value, that requires the introduction of antiglaucoma drops or surgical intervention at any time, associated with visual field loss and/or optic nerve changes. In patients with pre-existing glaucoma, uncontrolled IOP with the original treatment regime that requires an “escalation of treatment” after corneal surgery is enough to make the diagnosis (Al-Mohaimeed et al., 2007; Karadag et al., 2010; Olson and Kaufman, 1977).

The prevalence of glaucoma after PKP varies widely in the literature; it has been reported to vary among 10–53% (Al-Mohaimeed et al., 2007). This large range can be attributed to factors such as surgical techniques, surgical indications, and pre-existing conditions/indication for surgery (aphakia, pseudophakia, previous PKP, previous trauma, previous herpes simplex keratitis, or keratoconus).

Several preoperative risk factors for post-PKP-associated glaucoma have been reported to include young patient age, history of pre-existing glaucoma, pseudophakia, or aphakia, smaller recipient trephination, previous PKP, and a perforated corneal ulcer with the presence of adherent leukoma (Al-Mohaimeed et al., 2007; Chien et al., 1993; Huber et al., 2013; Irvine and Kaufman, 1969; Karesh and Nirankari, 1983). Preoperative existing glaucoma has been identified as the major risk factor for post-PKP glaucoma (Goldberg et al., 1981; Irvine and Kaufman, 1969).

Steroids usage remains the main cause of post-PKP glaucoma (Goldberg et al., 1981). However, a role in glaucoma after PKP can also be played by changes in the iridocorneal anatomy, due to a collapse and distortion of the trabecular meshwork. This subsequently increases aqueous outflow resistance. The anterior chamber angle distortion can be related to different aspects of the corneal surgery, in particular tight suturing, undersized graft, iatrogenic injury of the iridocorneal angle, development of peripheral synechiae, or postoperative inflammation (Goldberg et al., 1981).

The development of anterior and posterior synechiae can be responsible for trabecular distortion along with direct trabecular obstruction decreasing aqueous outflow. In a recent published article, Dada et al. (2008b) reported the UBM findings in 31 eyes affected by post-PKP glaucoma with mean reported IOP of 35.5 ± 5.8 mmHg (range 26–52 mmHg). In their cohort, 96.7% of eyes had peripheral anterior synechiae (PAS) along with 41.9% with graft–host junction synechiae (Dada et al., 2008b).

An attractive theory has been postulated by Zimmerman et al. (1978) to explain post-PKP glaucoma in aphakic eyes. Those eyes would be more prone to develop postoperative glaucoma due to a collapse of the trabecular meshwork, which occurs because of a loss of support of the iridocorneal angle. The theory is that the trabeculum needs anterior and posterior structural support—this requires the integrity of
lens/ciliary body complex support while the anterior support is given by the Descemet’s membrane. Both of these frameworks work as scaffolding structures; however, in PKP, the Descemet’s membrane is cut during the surgery, for the entire 360°. In aphakia patients undergoing PKP, both Descemet’s and lens/ciliary body complex are disrupted with lack of support for the iridocorneal angle and this will lead to partial trabecular collapse and subsequent obstruction of aqueous outflow.

Furthermore, Olson and Kaufman (1977) developed a mathematical model to predict factors for angle distortion in PKP, potentially leading to trabecular meshwork distortion, and a subsequently increased postoperative glaucoma risk.

The diagnosis of post-PKP glaucoma can adversely affect graft survival as reported by Ing et al. with only 58% of graft survival in patients with pre-existing glaucoma versus 80% in patients without glaucoma 10 years postoperatively (Ing et al., 1998). Similarly, in a different patient cohort, Reinhard et al. described a 3-year graft survival rate of 71% in patients with a history of glaucoma compared to 89% in patients without pre-existing glaucoma (Reinhard et al., 1997). Al-Mohaimeed et al. (2007) reported in a cohort study of 715 eyes that diagnosis of post-PKP glaucoma was associated with significantly poorer visual acuity and poorer graft survival rates compared with eyes without postoperative OHT.

Diagnosing and monitoring PKP-associated glaucoma is not always simple due to the decreased reliability of IOP measurements after corneal graft. Corneal irregularity, absence of corneal epithelium soon after the surgery and the presence of postoperative edema or scar formation, can make difficult to measure IOP with Goldmann applanation techniques. Indeed, the use of different instruments for IOP measurements should be considered, such as the Tono-Pen or the dynamic contour tonometer (DCT) (Dada et al., 2008a). The latter called also contour-matched tonometer has a concave tip surface that allows the cornea to assume its natural shape with only minimal distortion. DCT has reported to measure IOP independently of the corneal thickness within certain ranges of IOP (Kaufmann et al., 2004).

4 GLAUCOMA RISK AND DEEP ANTERIOR LAMELLAR KERATOPLASTY

DALK procedures aim to expose the recipient Descemet membrane finding a clear plane with uniform thickness (Anwar and Teichmann, 2002; Melles et al., 1999a; Sugita and Kondo, 1997).

DALK can be divided into Descemetic DALK (d-DALK) and pre-Descemetic DALK (pd-DALK). In d-DALK, the dissection plane is the clear Descemet membrane without any recipient stroma. In pd-DALK, the dissection plane is above the Descemet membrane and includes a variable amount of overlying corneal stroma. While different variations of pd-DALK techniques have been described (Melles et al., 1999b; Sugita and Kondo, 1997), the most used effective technique to perform d-DALK is the “big bubble” technique originally described by Anwar and Teichmann (2002).
Awan et al. (2010) reported an incidence of glaucoma in 17% of patients undergoing DALK for corneal scarring secondary to herpes simplex keratitis. Zhang et al. (2013) compared 5-year outcomes of DALK and PKP surgery for patients with keratoconus. The main difference in terms of the postoperative management was related to antirejection steroid regimen. Patients who underwent DALK (75 eyes) received 6 months of steroid treatment minimum postsurgery compared to 12 months minimum in the PKP group (52 eyes). At the last follow-up, no rejection episodes were recorded in the DALK group; 7.7% of the PKP group suffered endothelial rejection. Furthermore, none of the eyes in the DALK group required antiglaucoma treatment, while 46% (24 eyes) in the PKP group developed OHT attributed to steroid use. Five of these eyes required glaucoma surgery.

Musa et al. published the outcomes of 69 eyes undergoing DALK mainly for keratoconus. The authors found temporary steroid-induced OHT in 12 eyes. Three eyes required a single antiglaucoma drop and one of these three had a history of pre-existing glaucoma. The average IOP at the final follow-up visit for all patients was not statistically significantly different from the preoperative IOP (Musa et al., 2012).

DALK surgery allows a reduced postoperative steroid drops regimen compared with PKP thus reducing risk of glaucoma. The lack of Descemet’s membrane disruption with DALK also minimizes the distortion of the drainage angle that can occur after PKP thus leading to less risk of glaucoma according to the Zimmerman’s theory (Zimmerman et al., 1978).

5 GLAUCOMA RISK AND DESCemet STRIPPING-AUTOMATED ENDOthelial KERATOPlastY

The Eye Bank Association of America reported an increase in the number of endothelial transplants—from 1429 to 17,468 between 2005 and 2008 with a further increase to 23,465 in 2013 (Eye Bank Association of America, 2013).

Descemet stripping-automated endothelial keratoplasty has rapidly gained popularity as a first choice treatment modality for endothelial diseases, such as Fuchs endothelial dystrophy and bullous keratopathy, due to fast visual recovery, better corneal tectonic stability, and improved visual outcomes compared with PKP—along with a lower graft rejection rate (Lee et al., 2009). DSAEK also appears to be superior to PKP in terms of risk of glaucoma development. In a retrospective study, Kosker et al. analyzed the postoperative results of 15 patients that underwent PKP in one eye and DSAEK in the fellow eye for bilateral Fuchs dystrophy. The result was that 5 out of the 15 PKP developed postoperative glaucoma, compared with only 1 DSAEK eye (Kosker et al., 2013).

The American Academy of Ophthalmology DSAEK evaluation in 2009 concluded that the frequency of glaucoma as a complication after DSAEK varied between 0% and 15% from 23 studies with 3–18 months of follow-up (Lee et al., 2009). Vajaranant et al. conducted a retrospective study of 400 DSAEK procedures, reporting an incidence of IOP elevation in 35% of patients with no pre-existing
glaucoma, and in 44% of patients with pre-existing glaucoma. This was attributed mainly to steroid drop use. The authors reported that most of the patients managed well with an increase in glaucoma medications, tapering steroid drops or switching antirejection treatment to less potent topical steroids (Vajaranant et al., 2009).

DSAEK has a double peak in the incidence of glaucoma. In the early postoperative period, the common causes of glaucoma are mainly surgical related: (a) the presence of remaining ophthalmic viscoelastic device (OVD) in the anterior chamber, and (b) the pupillary block mechanism (peculiar of EK procedures) that can be produced by the bubble of air being left in the anterior chamber (to help the graft to remain in place). Usually, an iridectomy is performed inferiorly at the end of surgery to avoid air-induced pupil block. The second peak of glaucoma is observed months after the surgery and relates to steroid use—this seems to be the most common cause of elevated IOP after DSAEK with a reported incidence as high as 18.6% (Maier et al., 2013; Vajaranant et al., 2009).

Like in any graft surgery, pre-existing glaucoma greatly increases the risk of post-graft IOP elevation, with potential glaucoma exacerbation (Allen et al., 2010; Maier et al., 2013).

Positive history of glaucoma does also have a negative impact on long-term endothelial graft survival (Fig. 1). Anshu et al. carried out a long-term DSAEK graft survival study and described risk factors for graft survival in eyes with pre-existing glaucoma. The authors highlighted that graft survival at the 5-year follow-up was significantly lower in eyes with prior glaucoma surgery, particularly in eyes that had undergone glaucoma drainage device implantation prior to graft surgery (Anshu et al., 2012a).

**FIGURE 1**
One day post-DSAEK surgery in eye with previous glaucoma drainage device implant (red (dark gray in the print version) arrow). Endothelial graft in place (white arrow).
In conclusion, EK does have a lower risk of glaucoma than PKP and also the lesser disruption of the ocular surface with EK make postoperative IOPs measurement significant easier and reliable compared with PKP.

After DSAEK, the postoperative corneal thickness is increased by the addition of the graft posteriorly. A previous study reported an average corneal thickness of 690 ± 77 µm after an endothelial graft (Price and Price, 2006). Goldmann tonometry is calibrated to give reliable values for a mean corneal thickness of 520 µm (Whitacre and Stein, 1993) and therefore measurements could be less accurate for very thick corneas—IOP values can be theoretically falsely increased in case of EK where some tissue is added posteriorly to the recipient cornea (Whitacre and Stein, 1993). Vajaranant et al. (2008) compared IOP measurement after DSAEK with three different types of equipment—Goldmann applanation tonometry, pneumotonometry, and DCT and did not find a significant difference between the IOP measurements with the different devices. Another study confirmed that despite the increase in corneal thickness after DSAEK, Goldmann applanation tonometry did not show falsely elevated IOP measurements (Clemmensen and Hjortdal, 2014).

6 Glaucoma Risk and Descemet Membrane Endothelial Keratoplasty

The latest evolution of EK is DMEK. Melles first described DMEK in 2006 (Melles et al., 2006, 2008). This technique is now becoming widespread and is overcoming DSAEK for the treatment of endothelial dysfunction, given its advantages in terms of faster visual recovery, decreased risk of graft rejection (Anshu et al., 2012b), and possibly fewer postoperative complications including reduced risk of glaucoma (Anshu et al., 2012b; Guerra et al., 2011a).

Naveiras et al. (2012) analyzed cases of glaucoma in a series of 275 eyes that had undergone DMEK surgery. They found that glaucoma, defined as an IOP >24 mmHg or an elevation of >10 mmHg above the preoperative levels, was diagnosed in 18 eyes (6.5%). Seven eyes (2.5%) had an exacerbation of pre-existing glaucoma and 11 eyes (4.0%) were diagnosed with de novo postoperative raised IOP after DMEK. In eyes with pre-existing glaucoma, the raised IOP was attributed mainly to an exacerbation of primary glaucoma or a steroid response while, in eyes with de novo glaucoma, the causes of raised IOP were mainly pupillary block due to air bubble left in the anterior chamber and steroid-induced glaucoma. In all cases of pupillary block, this was resolved promptly (and with no recurrence) with pupil dilatation, short-term antiglaucoma drops or oral acetazolamide, and with appropriate patients posturing.

In a prospective randomized study, Price et al. (2014) reported the results of 325 eyes that had undergone DMEK surgery. Eyes treated with weak steroids such as fluorometholone 0.1% (161 eyes) showed to have less risk of postoperative OHT when compared with eyes treated with prednisolone acetate 1% (6.1% vs. 21.9%, respectively) without substantially increasing the risk of immunologic graft rejection
episodes. The extremely low rejection risk reported with DMEK procedure (Anshu et al., 2012b; Guerra et al., 2011a; Price et al., 2009b) provides the possibility to reduce the postoperative topical corticosteroid strength and thus significantly reduce the risk of post-graft glaucoma without considerably increasing the hazard of immunologic graft rejection episodes.

7 POST-CORNEAL GRAFT GLAUCOMA TREATMENT

In cases of post-corneal transplant glaucoma, the goal of treatment is to normalize the IOP. For this purpose, the use of topical medication is the first-line treatment (Al-Mohaimeed et al., 2007; Dada et al., 2008a). In case of steroid responsive glaucoma reported as the most frequent cause of a post-corneal graft OHT (Al-Mohaimeed et al., 2007), the obvious treatment is to start an antiglaucoma treatment and reduce steroid dosage to the minimum required or attempting steroids replacement using less IOP increasing topical agents such as fluorometholone or loteprednol (Price et al., 2014).

7.1 MEDICAL TREATMENT

The first-line treatment involves topical antiglaucoma drops and does not differ from general glaucoma medical treatment or in different corneal graft techniques. Glaucoma drops toxicity is more likely in post-graft patients and especially after PKP. Preservative-free antiglaucoma drops when available should be preferred in presence of ocular surface problems and especially after PKP (Al-Mahmood et al., 2012; Al-Mohaimeed et al., 2007; Dada et al., 2008a; Gupta et al., 2014; Huber et al., 2013).

Al-Mahmood et al. (2012) have highlighted how the use of beta-adrenergic blockers and alpha-2-adrenergic agonist drugs can exacerbate dry eyes. Further, alpha-2-adrenergic agonist can also lead to allergic reaction and superficial punctate keratopathy (Tanna et al., 2010). The protracted use of topical carbonic anhydrase inhibitors has been reported to lead to graft decompensation in the presence of not healthy corneal endothelial status (Konowal et al., 1999). Prostaglandin analogs should also be used with caution as they may lead to increased intraocular inflammation and cystoid macular edema especially in aphakia (Ayyala et al., 1998), and reactivation of herpes simplex keratitis in patients with a previous history of herpetic keratitis (Wand et al., 1999).

7.2 SURGICAL TREATMENT

Surgical management becomes mandatory when the target pressure is not achieved with maximal topical therapy. Conventional trabeculectomy is less effective in eyes with a previous PKP, due to persistent conjunctival inflammation and scarring with a consequent increased risk of bleb failure (Skuta et al., 1992). The use of
antimetabolite drugs is common; Chowers and Ticho (1999) have reported good IOP control success rates with mitomycin C trabeculectomy in patients with post-PKP glaucoma. The use of drainage devices has improved IOP control after PKP. Drainage device implantation can help glaucoma control (Kwon et al., 2001; Al-Torbak, 2003). Glaucoma drainage device implantation for post-PKP appears to have possibly better outcomes at 1 year, compared to trabeculectomy (Almousa et al., 2013; Knape et al., 2012).

Cyclodestructive procedures can also be an option in case of glaucoma post-PKP (Al-Mahmood et al., 2012; Ocakoglu et al., 2005). Cyclocryotherapy, transscleral cyclophotocoagulation with diode or krypton laser aim to control the IOP by decreasing aqueous humor production destroying part of the ciliary body (Dada et al., 2008a). Despite the good results in controlling IOP, cyclodestructive procedure can be associated to severe complications such as hypotony, persistent inflammation, macular edema, corneal decompensation, choroidal and retinal detachment, sympathetic ophthalmia, and sometimes phthisis bulbi (Gupta et al., 2014), and therefore represents the last line of treatment. Tandon et al. (2014) published recently a meta-analysis on post-PKP glaucoma and directly compared the affect of trabeculectomy, cyclophotocoagulation, and glaucoma drainage device on IOP control and corneal graft survival. The analysis of 266 eyes showed that trabeculectomy led to an IOP reduction of 13.6 mmHg compared with 20.4 mmHg with cyclophotocoagulation and 20.2 mmHg with glaucoma drainage device. However, the failure rate for glaucoma surgery was highest after trabeculectomy at 37% compared with 20.7% after cyclophotocoagulation and 16% after drainage device implant with statistically significant difference. The percentage of patients who experienced worsening of vision was the highest after cyclophotocoagulation (26%) and the least with drainage device implant (20%). This study appears to confirm that drainage device surgery leads to better outcomes after corneal transplant surgery.

8 KERATOPROSTHESIS

In case of multiple failed corneal transplants or severe ocular disease, such as vascularized corneal scars, severe chemical injuries, ocular cicatrizing conditions such as Stevens–Johnson syndrome, the use of artificial corneas or keratoprosthesis (Kpro) should be considered. Different type of Kpro are in use and the most widely used are the Boston keratoprosthesis (types I and II), and the modified osteo-odontokeratoprosthesis (MOOKP) (Hicks et al., 2000). The most worldwide Kpro used is the Boston type I (Tan et al., 2012). The Boston type I Kpro consists of front and back plastic (polymethylmethacrylate) plates assembled together with a donor cornea as support and then sutured in place as in a PKP fashion (Tan et al., 2012). Despite the good short-term visual result after Kpro implant, long-term visual prognosis is limited by glaucoma and other complications (Bradley et al., 2009). Being the Kpro implant a procedure that replaces the natural cornea with a prosthesis, the traditional applanation instrument to measure the IOP cannot be used and digital eye palpation
is the primarily method adopted for IOP evaluation. Tono-Pen can also be used at the limbus level for an IOP measurement and compared with values of the fellow eye at the same limbus level (Al-Mahmood et al., 2012). Moreover, the progression of glaucoma damage is difficult to evaluate with visual field testing and consequently the use of optical coherence tomography (OCT) has been proposed to evaluate the optic nerve head and retinal nerve fiber layer (Chew et al., 2009). In addition to the difficulty in IOP measurement, it has been reported that patient candidate to have a Kpro implant have high prevalence of glaucoma (36–76% (Al-Mahmood et al., 2012)) due to the long-standing disease or repeated previous failed corneal graft procedures.

The main etiology for post-Kpro implant glaucoma is an iridocorneal angle distortion related to previous repeated surgeries along with crowding anterior segment (AS) by the large Kpro implant and the lens and iris removal leading to distortion and collapsing of trabecular meshwork (Al-Mahmood et al., 2012). Qian et al. (2015) have recently published an interesting prospecting pilot study evaluating the role of AS-OCT in 20 eyes of 20 patients which underwent Boston type I Kpro implant. They recorded postoperative visual acuity, glaucoma progression, and anatomic angle changes on AS-OCT in term of angle closure, iris-backplate touch, and PAS. Fourteen patients out of 20 (70%) were already diagnosed and treated for glaucoma before Kpro surgery, with 7 of 14 patients having previously undergone 1 or more IOP-lowering surgeries. After Kpro implantation, one new diagnosis of glaucoma was made. Anterior segment-OCT images showed that 30% of eyes already had 360° closed angles and synechiae before surgery. The presence of total angle closure and PAS progressively increased at each follow-up although the most drastic increase presented at 3 months after surgery. Eyes that underwent PKP before Kpro surgery had more PAS and angle closure before Kpro implant and also higher progression of PAS formation after Kpro implant. Although many patients have evidence of angle closure and distortion before Kpro implantation, these almost invariably worsen after Kpro implantation, suggesting that Kpro surgery itself plays a causal role on anatomic changes and glaucoma development.

A recent retrospective multicenter review of patients who underwent Kpro implantation surgery (Srikumaran et al., 2014) reported the outcome of 139 eyes of 133 patients with a mean of follow-up of 46.7 months (range, 6 weeks to 8.7 years) at five tertiary referral centers in the United States. The indication for Kpro surgery was prior donor graft failure in the majority of eyes (73%) and 58.3% of eyes had a known history of glaucoma. Approximately, one-third of the eyes (30.4%) had received prior glaucoma surgery. Twenty-five percent of the eyes required a concomitant anterior vitrectomy, and more than one-fifth of the eyes (21%) underwent simultaneous glaucoma surgery. The most common postoperative complication reported was formation of a retro-prosthetic membrane with a cumulative incidence of almost 50%. The second most frequent complication was glaucoma development or exacerbation of pre-existing glaucoma in more than 1/3 of eyes. The 21.6% of eyes required surgical intervention for glaucoma management in the form of tube shunt surgery or diode ciliary body ablation. Ciolino et al. (2013) reported results of
“Boston Keratoprosthesis Type 1 Multicenter Study” consisting of a large prospective cohort study gathering data on the 300 Boston Kpro implants in 30 patients by 19 surgeons at 18 medical centers. The average duration of follow-up was 17.1 ± 14.8 months, with a range of 1 week to more than 6.1 years. Authors reported that eyes which had undergone glaucoma surgery before keratoprosthesis implantation had a lower failure rate (2.9%) in comparison with those that had not undergone prior glaucoma surgery. It has also been advocated a simultaneous or prior glaucoma surgery in term of glaucoma drainage device implantation or cyclodestructive procedure unless the patient has no history of glaucoma and with normal IOPs (Al-Mahmood et al., 2012).

In conclusion, glaucoma is a common sight-threatening complication after Kpro implant. Glaucoma management after Kpro is not only very challenging but also can lead to poor visual outcomes.

9 LASER-ASSISTED IN SITU KERATOMILEUSIS—INTERFACE FLUID SYNDROME

Laser-assisted in situ keratomileusis (LASIK) is the most popular laser refractive surgery procedure performed worldwide due to fast visual recovery, reduced post-operative pain compared with photorefractive keratectomy (PRK), and reliable outcomes. However, this procedure is technically somewhat more complex than laser surface ablation procedures (PRK, laser-assisted subepithelial keratectomy—LASEK, and epithelial laser in Situ keratomileusis—EPiLASIK) and involves the creation of a corneal flap. In contemporary LASIK surgery, the flap is created using a femtosecond laser. LASIK flap complications are very rare but can unfortunately occur causing sight damage (Jutley et al., 2014; Moshirfar et al., 2010; Shah and Melki, 2014).

Since steroids are used after laser refractive surgery steroid-related glaucoma can occur (Levy et al., 1997). Given the changed corneal thickness after laser refractive surgery, the measurement of IOP with Goldmann applanation tonometry is often not fully reliable post-LASIK (Fournier et al., 1998).

A unique steroid-induced high-pressure complication after LASIK surgery is associated to the chronic presence of fluid in the interface between the flap and the stroma—known as interface fluid syndrome (IFS). This syndrome seems to be related to an undetected increase in IOP that may occur in the first days or weeks after flap creation mostly in steroid-responder patients.

Excess fluid, as a result of increased IOP, can build up in the interface space subsequent to the impairment of the endothelial cell pump and can lead to corneal edema. Subsequently, the fluid remains entrapped in the virtual space between the corneal stroma and the flap. In the early stages of the disease, IFS can mimic other post-LASIK inflammatory conditions such as diffuse lamellar keratitis. This misdiagnosis can lead clinicians to wrongly prescribe more steroid drops, further raising the IOP and continuing the pathological vicious circle (Bamashmus and Saleh, 2013;
Hamilton et al., 2002). The increased IOP can be misdiagnosed with the Goldmann tonometer due to the “airbag effect” of fluid under the corneal flap during applanation. The diagnosis is made clinically with slit lamp observation of a fluid pocket at the LASIK flap interface and confirmed with an AS-OCT (Senthil et al., 2010). With the aid of a Tono-Pen, the IOP can be measured outside the field of the flap and the raised IOP can be confirmed. The management of this unusual complication of steroid-induced high-pressure response after LASIK is obvious and involves discontinuing steroids and starting topical antiglaucoma treatments to avoid glaucoma damage.

10 URRETS-ZAVALIA SYNDROME

Urrets-Zavalia syndrome (UZS) was described for the first time by Urrets Zavalia in 1963 as a rare postoperative complication after PKP surgery in patients with keratoconus (Urrets Zavalia, 1963). This syndrome consists of a fixed dilated pupil, iris atrophy, and secondary glaucoma (Fig. 2). Initially, Alberto Urrets-Zavalia proposed that topical mydriatics in patients with keratoconus undergoing PKP could be a causative factor. Zavalia suggested that abnormal angle structures may predispose patients with keratoconus undergoing PKP to the formation of PAS and the development of an acute rise in IOP after receiving strong mydriatic drops (Urrets Zavalia, 1963). Urrets-Zavalia’s case series estimated that this syndrome occurs in 2.2% of keratoconus patients undergoing PKP (Urrets Zavalia, 1963).

Although this syndrome was first described after PKP surgery, with time surgeons have observed this condition after almost any type of intraocular surgery including DSAEK, DALK, cataract, and glaucoma procedures and even phakic

![Fixed dilated pupil (Urrets-Zavalia syndrome) after penetrating keratoplasty.](image)

*Courtesy of Professor John Dart, Moorfields Eye Hospital, London, UK.*
intraocular lens implantation surgery (Anwar et al., 2012; Maurino et al., 2002; Minasian and Ayliffe, 2002; Yuzbasioglu et al., 2006). The exact etiology of the syndrome is still uncertain; some mechanisms such as pupillary block (Davies and Ruben, 1975) after an intracameral injection of air/gas (Maurino et al., 2002), iris ischemia, and abnormalities of the iris (Gasset, 1977) have been postulated as possible causes. It has also been suggested that iris ischemia may develop if the iris is compressed between the lens and the cornea during surgery (Davies and Ruben, 1975).

Tuft and Buckley (1995) suggested that in the presence of raised IOP, the low ocular rigidity of the keratoconic eye permits occlusion of the vessels at the root of iris within the sclera, which results in iris ischemia while preserving ciliary body function. Davis and Ruben noted that the condition is more common in the absence of a peripheral iridectomy and proposed a mechanism of relative pupillary block (Davies and Ruben, 1975).

Figueiredo et al. (2013) reported a significant correlation between post-PKP IOP elevation and iris ischemia, documented with indocyanine green iris angiography in keratoconic patients. The authors recommended tight control of IOP after PKP, mainly with meticulous viscoelastic removal at the end of surgery.

Maurino et al. (2002) described the first cases of UZS after DALK and speculated that if air/gas is left in the anterior chamber, a surgical peripheral iridectomy and/or mydriatic drops could prevent pupillary block and UZS. It was suggested that the patient should lie in a supine position to keep the air/gas bubble far from the pupillary aperture thus avoiding pupil block, and that in the first few hours postoperatively the IOP should be closely monitored. Timely diagnosis and treatment may decrease the risk of further complications, such as posterior synechiae and optic nerve head damage as a result of high IOP.

The prevention of UZS is difficult because the precise causes are unclear; however, some strategies have been proposed. Preoperatively, a Yag laser iridotomy can prevent a pupillary block and subsequent iris vessel ischemia (Spierer and Lazar, 2014). Intraoperatively, anterior chamber should be kept deep and formed to prevent iris synechiae formation (Davies and Ruben, 1975) avoiding iris surgical trauma (Flament et al., 1984). We believe that to prevent UZS, a tight postoperative IOP control is absolutely mandatory.

11 CONCLUSIONS

Glaucoma is a well-known complication of corneal graft surgery and can be a long-term cause of graft failure and visual loss. The ACGR (Anonymous, 1993) has attributed graft failure to glaucoma in 11% of patients and other studies have shown even higher graft failure rates in association with glaucoma (Reinhard et al., 1997). Furthermore, chronic or acute highly IOP elevation can potentially compromise the graft endothelial function and can lead to endothelial cell loss of 10–33% (Huber et al., 2013).
The two major risk factors for developing glaucoma after any type of corneal graft are (a) the antirejection steroid treatment and (b) any pre-existing glaucoma.

The recent advances in corneal graft surgery with the introduction of new lamellar layer selective corneal graft techniques as DALK, DSAEK, and DMEK have shown excellent postoperative results (Cheng et al., 2013; Keane et al., 2014; Price and Price, 2013; Price et al., 2013; Sogutlu Sari et al., 2013) along with reduced risk of sight-threatening glaucoma compared with PKP (Haddadin and Chodosh, 2014).

Reduced graft rejection and graft failure risk (Anshu et al., 2012b; Dapena et al., 2011) is one of the main advantages of the lamellar techniques. The lamellar techniques allow lesser use of postoperative steroids regime, thereby decreasing the risk of developing postoperative steroid-related glaucoma. The reduced use of antirejection steroid treatments in layer selective keratoplasty appears to be the most important factor in reducing post-graft glaucoma (Al-Mahmood et al., 2012; Anshu et al., 2012b; Armaly, 1963; Cheng et al., 2013; Dada et al., 2008a; Price et al., 2014). Another important advantage of layer selective transplant versus PKP is the less invasive surgical nature of the lamellar techniques with reduced intraocular damage leading to minimal trabecular meshwork disruption (Zimmerman theory (Zimmerman et al., 1978)).

Compared with PKP, diagnosis and management of post-corneal graft glaucoma can be simpler after lamellar corneal graft due the lesser negative effects on ocular surface, corneal shape, and thickness that make measuring IOP more reliable as well as diagnosing and monitoring glaucoma.

Nonetheless, lamellar corneal surgery techniques (DALK, DSAEK, DMEK) do have some specific glaucoma risk mechanism and especially known is the risk of pupillary block glaucoma after EK (Naveiras et al., 2012).

In conclusion, glaucoma is still common after corneal graft surgery but the evolution from perforating graft techniques to lamellar techniques appears to have reduced its risk and incidence. Patients must be warned of glaucoma risks after corneal transplant surgery especially in cases of pre-existing glaucoma.

REFERENCES


