Purpose: To evaluate the gonioscopic changes in patients receiving Descemet’s stripping endothelial keratoplasty (DSEK) without pre-existing ocular hypertension (OHT) and to report its correlation with post-surgery OHT, graft survival, and visual outcomes. Methods: Adult patients who underwent DSEK surgery from April 2014 to March 2018 with at least 2 years of follow-up were analyzed in this retrospective study. Demographic details, indication of DSEK, necessary anterior and posterior segment findings, and the post-DSEK OHT details were documented. Results: A total of 58 patients (23 males and 35 females) with a mean age of 61.44 ± 8.8 years were included in the study. The most common etiology for DSEK surgery was pseudophakic bullous keratopathy in 47 eyes (81.03%). A total of 22.41% (13/58) eyes showed elevated intra-ocular pressure (IOP) following DSEK surgery. The most common cause of IOP elevation was steroid-induced OHT in seven eyes (12.06%). Gonioscopy examination revealed areas of peripheral anterior synechiae (PAS) in 17 (29.3%) eyes. OHT was found in 4/17 (23.5%) having PAS. Three of these cases required trabeculectomy + goniopunctureysis (GSL), and the fourth case required GSL alone to control IOP. These four cases also required repeat DSEK for failed graft. The mean pre-operative corrected visual acuity was 1.62 logMAR (range 1.17–1.77), which gradually improved to 0.79 logMAR (range 0.3–1.77) after 2 years (p < 0.00001). Conclusion: PAS was found to be an important factor associated with post-DSEK ocular hypertension in our study. OHT in PAS cases required definitive surgical treatments to control IOP. It adversely affected the graft survival and in turn affected visual outcomes also.

Key words: Descemet’s stripping endothelial keratoplasty, gonioscopy, peripheral anterior synechiae, post-DSEK glaucoma, trabeculectomy

Post-operative ocular hypertension (OHT) remains an important complication after Descemet’s stripping endothelial keratoplasty (DSEK). Although DSEK is a less invasive lamellar surgical technique, it can be complicated with secondary OHT in patients with or without pre-existing glaucoma. Those with pre-existing glaucoma are more likely to need steroid reduction or topical anti-glaucoma medication (AGM) to control the intra-ocular pressure (IOP). IOP elevation after DSEK also affects the visual outcomes by damaging optic nerve and graft survival in these patients. The reported incidences of IOP elevation are 28% to 39% after DSEK surgery during the first post-operative year. Associated risk factors are a graft size of more than 8.5 mm, large air bubbles in the anterior chamber (AC), and steroid-related mechanisms. Previous studies have reported that pre-existing OHT, pseudophakic or aphakic bullous keratopathy, and steroid-induced mechanisms are most consistently found risk factors in post DSEK-OHT. The presence of peripheral anterior synechiae (PAS) has been hypothesized to be an independent risk factor for post-surgery OHT, but there is paucity of literature which highlights such angle structures seen on gonioscopy in post-DSEK patients.

In the present study, we have evaluated incidence and management of OHT after DSEK surgery. As prior glaucoma can be worsened after surgery clouding the true relation of DSEK and ocular hypertension, we included patients without any history of ocular hypertension or glaucoma. The further aim of our study was to evaluate the gonioscopic changes in the eyes of post-DSEK patients and to report the correlation with ocular hypertension, graft survival, and visual outcomes.

Methods

This was a retrospective, single-center and analytical study performed at a tertiary eye care center in Central India. The study was initiated after approval from the institutional review board.
board and conducted in accordance with the standards of the Helsinki Declaration. All the treatments and surgeries were performed after obtaining detailed informed written consent.

Medical records of 171 adult patients who underwent DSEK surgery between April 2014 and March 2018 were analyzed. All the cases were carefully inspected, and glaucoma and angle-related details were noted. We included only those cases without any history of OHT/glaucoma. Any evidence of PAS prior to DSEK also warranted exclusion from the study. Proper documentation of the angle structure with at least 2 years of follow-up was necessary for the inclusion in the study.

Demographic details, indications of DSEKs surgery, prior history of OHT, medications, and the post-DSEK treatment were documented properly. Visual acuity, IOP measurement, and graft clarity were assessed at every visit. Visual acuity was measured using Snellen chart. IOP was measured using a Goldmann applanation tonometer. Dynamic and indentation gonioscopy was performed using Sussman four mirror goniolenses yearly or whenever raised IOP was documented. Areas of PAS were noted and broadly categorized into three groups: 1) Focal/scattered PAS involving $<90^\circ$, 2) $>90^\circ$ to $180^\circ$ PAS, and 3) more than $180^\circ$ PAS.

OHT was defined as IOP of $>21$ mm Hg. The term ‘Glaucoma’ was used whenever OHT was associated with evidence of optic nerve damage in the form of an increased vertical cupdisc ratio from the previously documented value. OHT/glaucoma was further categorized according to etiopathogenesis into three categories: 1) pupillary block – transient IOP elevation in the first 2 days associated with air bubbles in the anterior chamber, 2) steroid-induced – when IOP reduction was observed after tapering steroids or switching to less potent medications, and 3) synechial angle closure – when OHT was noticed along with PAS in gonioscopy.

Surgical technique of DSEK
Surgeries were performed by a single experienced corneal surgeon. All cases were performed under peribulbar anesthesia. Descemeto-rhexis was made of size 8 mm in the viscoelastic filled eye, followed by thorough wash. For the graft preparation, the donor cornea was mounted on an artificial anterior chamber and lamellar dissection was performed at a depth to yield a graft thickness of 150–190 microns. Graft was inserted into the anterior chamber as a taco fold through a scleral incision of 5 mm superiorly with the help of a bent 26-gauge needle. Single 10-0 nylon suture was applied at the tunnel at this stage. The graft was unfolded and positioned in the center by taping over the cornea. Graft was secured in place with a full chamber air bubble. After 10 minutes, the air bubble was approximately reduced by 20% along with intra-cameral injection of moxifloxacin (0.5% eyedrop, Vigamox, Alcon, Texas). Patients were reviewed after 2 hours on slit lamp and advised topical eyedrops prednisolone (1% Predforte, Allergan, Ireland) six times, moxifloxacin (0.5%, Vigamox, Alcon, Texas) four times, and timolol (0.5%, Sun Pharma, Mumbai, India) twice a day for 15 days. Cataract extraction with intra-ocular lens implantation was also performed in cases of Fuchs’ endothelial dystrophy associated with cataract.

Post-operative follow-up was performed at the intervals of 1 week, 1 month, 3 months, 6 months, and 6 monthly thereafter. Follow-up varied from patient to patient depending upon the healing course, graft status, and IOP.

Treatment of ocular hypertension after DSEK
Fig. 1 outlines the proposed management scheme practiced at our institute. OHT in the first few post-operative days usually reflected pupillary block when associated with large air bubbles. Later on, suspicion of OHT was steroid response. For this, potent steroids were tapered or switched to less potent steroid-like loteprednol. Whenever raised IOP associated with PAS was refractory to AGMs, goniosynechiolysis (GSL) or trabeculectomy was performed. GSL alone was usually reserved for cases having $<180$ degrees of PAS. Intractable glaucoma with $>180$ degrees of PAS underwent trabeculectomy with GSL. Fig. 2 is a representative image of PAS in a DSEK-operated eye.

Statistical analysis
The statistical analysis was performed using IBM SPSS Statistics software 24.0.0.0. Microsoft Word and Excel (Microsoft corporation, USA) were used for data entry, and various charts were constructed using the same. Quantitative variables were presented as mean and standard deviation. Qualitative variables were presented as number and percentage. Parametric quantities such as pre- and post-DSEK IOP were compared using paired t-test. Pre- and post-DSEK logMAR visual acuities were compared using Wilcoxon rank test. Kaplan–Meier survival charts were generated for graft survival. A $P$ value of $<0.05$ was considered statistically significant.

Results
Out of 171 patients, 58 eyes of 58 patients were included in the study as per inclusion criteria. Twenty-three were males, and 35 were females, with a mean age of 61.44 ± 8.8 years. The underlying etiologies in patients who underwent DSEK surgery were pseudophakic bullous keratopathy (PBK)/aphakic bullous keratopathy (ABK) in 47 eyes (81.03%), Fuchs’ endothelial dystrophy (FED) in ten eyes (17.24%), and post-viral keratitis scar in one eye (1.7%). The mean pre-operative IOP was 16.12 ± 1.96 mm of Hg.

A total of 13/58 (22.4%) eyes showed elevated IOP in our series following DSEK surgery. The most common causes of IOP elevation were steroid-induced OHT in seven eyes (12.06%), followed by synechial angle closure in four eyes (6.9%), and pupillary block in two (3.4%). Three eyes having synechial angle closure also fell in the category of glaucoma as the vertical cup: the disc ratio worsened by $>0.2$.

Pupillary block hypertension cases could be managed successfully with 1-week treatment of an oral carbonic anhydrase inhibitor (Tab. Acetazolamide, 250 mg QID). In steroid responders, raised IOP was seen at 1–3 months post-operatively. The range of the IOP values was 24–45 mmHg. Maximum IOP rise was noted at 3 months. Four patients could be managed successfully with tapering of steroids alone (± steroid sparing agents). However, the remaining three cases required AGMs to control IOP. None of these cases developed graft failure. AGMs alone were not sufficient to control the IOP in four PAS-associated cases. The peak of the OHT was noticed at 6 months after DSEK in this sub-group. Two eyes underwent trabeculectomy + GSL (same sitting) 6 months after DSEK surgery. However, one eye each underwent GSL and trabeculectomy + GSL 8 months after DSEK. Line charts are mentioned in Fig. 3, which represent IOP trends and changes in different groups over the 2-year follow-up period.

Gonioscopy findings revealed focal PAS ($<90^\circ$) in 12 eyes (20.7%), 90–180$^\circ$ PAS in two eyes (3.4%), and $>180^\circ$ high PAS in three eyes (5.2%). OHT was found in 4/17 (23.5%) eyes having PAS. One patient in the 90–180$^\circ$ PAS group (1/2, 50%) had raised IOP which was managed with GSL. However, all the three patients of $>180^\circ$ PAS required trabeculectomy + GSL. Post trabeculectomy, two patients required timolol eyedrops (0.5%, twice a day) to bring IOP within normal ranges.
The Kaplan–Meier graft survival curve is presented in Fig. 4. After 2 years, clear grafts were observed in 53/58 eyes (91.37% survival); while graft failure was seen in only five eyes (8.6%). A high proportion of graft failure was seen in eyes with PAS (4/17). Out of the remaining 41 eyes without PAS, only one developed graft failure, possibly because of immunological rejection. Four cases of graft failure had increased IOP. Out of these four cases, three cases had >180 degree PAS, whereas one case had 90-180 degree PAS. This signifies association between degree of PAS and graft failure. All OHT-associated graft failure occurred during the first 6 months after DSEK surgery.

Discussion
In our study, we have evaluated the occurrence of OHT after DSEK surgery and its relation with PAS, management, and outcomes. The incidence of OHT was 22.4% in our series with 91.4% graft survival after 2 years. Steroids were the most
common culprit responsible for OHT; however, these cases could be managed easily with or without AGM. PAS-associated OHT however required additional trabeculectomy and GSL procedures. These four cases (originally having PBK/ABK) also developed graft failure.

DSEK is an established and commonly performed procedure for corneal pathologies related with endothelial dysfunctions. It is a less invasive surgery that selectively replaces the diseased corneal endothelium and Descemet’s membrane. Indications of DSEK include pseudophakic or aphakic bullous keratopathy, re-graft, post-viral keratitis corneal scar, keratoconus, and Fuchs’ endothelial dystrophy. The major indication of DSEK in our study was pseudophakic/aphakic bullous keratopathy in 81.3% cases. A similar trend was also seen in a study by Ugo de Sanetis et al. where 62% of ABK/PBK patients underwent endothelial keratoplasty. Droutsas et al. also noted preference of endothelial keratoplasty in 90% of bullous keratopathy patients.

Secondary OHT is a frequent complication after DSEK surgery with a reported incidence which varies between 28% to 35%. The incidence of OHT in our study was less than the that of the above-mentioned study, possibly because we included patients without a history of pre-existing OHT. Individuals with prior OHT have a higher incidence of post-DSEK OHT as reported by Maier et al. Similar to other studies, we also found higher incidence of steroid-induced OHT following DSEK. In these cases, OHT was evident right from the beginning and peaked at around 3 months. However, no long-term sequelae were noted, and all cases could be managed conservatively. It is often difficult switching to less potent steroid medication in the early post-operative period. One must weigh the benefits and risks associated with medications used and its impact on graft survival. Steroid sparring agents (e.g., cyclosporine eyedrop, 0.5%) may be used if steroids need to be tapered. If such a response is noted many months after surgery, switching to loteprednol/fluorometholone may be an acceptable alternative. Also, IOP elevation in such cases is temporary if noted and treated early. This signifies the importance of strict frequent follow-up visits.

Cheng et al. and Koenig et al. reported 3–5% cases of pupillary block OHT, similar to what we noted. Pupillary block occurs because of intra-cameral injection of large air bubbles to fixate the graft to posterior lamella. This type of IOP elevation is temporary and can be relieved by medications as noted in our cases. However, the prolonged presence of air bubbles behind the iris may lead to the formation of PAS, which in turn may cause glaucoma later on. Peripheral iridectomy prevents progression of these cases by preventing PAS formation. The incidence of pupillary block can be prevented by placing a freely mobile air bubble and putting cycloplegic drops at the end of the surgery as suggested by Terry et al. None of the pupillary block OHT patients developed PAS on gonioscopy in our series. Reducing the size of the air bubble at the end of the surgery also prevented significant elevation of IOP in our cases.

The damage to aqueous outflow mechanisms, loss of angle structures, and synechiae angle closure have also been proposed as factors leading to IOP elevation after DSEK similar to post-penetrating keratoplasty patients. PAS was found in 29.3% cases on gonioscopy in our study. Basak et al. reported five cases of late secondary angle closure OHT with 360° PAS in their series of 430 cases of DSEK. However, they have not analyzed the angle structure in all cases. Goniosynechiolysis cured the IOP elevation in one of our cases of PAS of <180° angle. We could not manage the OHT with AGMs alone in cases having >180° PAS, and all required trabeculectomy + GSL to control their IOP. The peak of the IOP levels was seen at around 6 months in these cases, which also coincided with graft failure occurrences.
The graft rejection/failure rate in DSEK cases varies between 0 and 12% with 2 years of follow-up in different studies. Ratanasit et al. reported 7.8% incidence of late graft rejection among 51 cases in their longest follow-up of >5 years. Our graft failure rates were also comparable with the above-mentioned studies. The failed DSEK cases could be managed by repeat DSEK surgery in all five cases in our series with good outcomes. In our study, no decentered grafts were noted during any point of time.

Previous histopathologic studies revealed that endothelial cell loss is the main cause of graft failure in DSEK. However, we have not analyzed the endothelial cell density in our study. OHT adversely affects the donor endothelial cells and increases the risk of re-DSEK surgery. Our four out of five graft failure cases had significant PAS associated OHT, which required surgery to control IOP as well. All these four cases initially had pseudophakic/aphakic bullous keratopathy. Anshu et al. in one of the largest studies, evaluated long-term survival of DSEK grafts. They noted excellent 5-year survival of 96% in patients without glaucoma. However, the survival drastically reduced to 25% and 59%, who needed a glaucoma drainage device and trabeculectomy, respectively. They also noted a significant risk of graft failure having an indication of pseudophakic or aphakic bullous keratopathy. Price et al. noted significantly poor graft survival in aphakic/pseudophakic corneal edema and those eyes that required glaucoma surgery. Lanxing Fu and Emma J Hollick noted that prior glaucoma, including glaucoma surgery, and re-grafts were important causes of graft failure. These results are thus strongly in accordance with our findings indicating the important role of glaucoma and indication of surgery leading to failure.

In our study, significant improvement was noted in the BCVA after 2 years of follow-up. Patients having OHT had significantly worse visual acuity and still achieved an acceptable mean value of 1.04 logMAR. The good functional outcomes in our study could be attributed to the early intervention, strict follow-up, and a properly tailored intervention approach for OHT and graft failure patients.

Talking about limitations of the study, first, endothelial counts were not available for all patients. Therefore, we could not analyze the impact of IOP on the graft cells objectively. We also could not establish the risk factors for PAS formation in our patients. Still, ours is a unique study which involved patients without any prior history of glaucoma. This in turn enabled us to detect the true relation of DSEK surgery and OHT. Also, we evaluated the angle structure in all our cases. This along with strict follow-up protocols gave us useful insights for the reasons behind OHT, time frames, and impacts on graft survival, which will help in the future deciding optimal treatment strategies.

**Conclusion**

In conclusion, steroid response is still the most common cause of OHT after DSEK surgery, which is seen early and can be easily managed conservatively. Synechial closure of the angle is also an important factor leading to often intractable
glaucoma which adversely affects the donor graft survival. Gonioscopy should be periodically performed after DSEK surgery to identify such cases early to achieve good anatomical and functional outcomes.

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Conflicts of interest
There are no conflicts of interest.

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