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Keratoplasty: are children missing out on the lamellar revolution—the 2023 Bowman Club, David L. Easty Lecture

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ABSTRACT

There has been a growing interest in lamellar keratoplasty over penetrating keratoplasty in the treatment of cornea diseases. Children, in particular, may benefit from lamellar keratoplasty due to faster visual recovery, better outcomes, fewer eye drops and earlier amblyopia treatment. This review aims to examine the trends, surgical techniques and outcomes in paediatric lamellar keratoplasty. Additionally, alternative treatment modalities to keratoplasty such as selective endothelium removal in Peters anomaly and ophthalmic non-steroidal anti-inflammatory drugs eyedrops in congenital hereditary endothelial dystrophy are also discussed.

INTRODUCTION

Lamellar keratoplasty has been growing in popularity as an alternative to penetrating keratoplasty (PK) in the treatment of various cornea diseases. With PK being an open sky procedure, it can be associated with significant sight threatening complications such as intraoperative suprachoroidal haemorrhage, lens and vitreous loss and postoperative complications such as suture infiltrates, endophthalmitis and glaucoma. With the recent advancements of laser systems, suture-less grafts and improved surgical equipment, there is an increase in anterior and posterior lamellar corneal transplantation surgeries performed worldwide. Lamellar keratoplasty, being a relatively closed-system procedure involving only diseased layers, is associated with reduced incidence of complications, faster recovery and better visual outcomes.[1 2] Importantly, it minimises the unnecessary replacement of unaffected healthy host cornea layers.

Anterior lamellar keratoplasty (ALK) involves partial replacement of anterior diseased stromal. Meanwhile, posterior lamellar keratoplasty, or endothelial keratoplasty (EK), such as Descemet stripping automated EK (DSAEK) and Descemet membrane endothelium keratoplasty (DMEK), replaces diseased endothelium.

In Singapore, recent trends indicate that among adult patients, EK has increasingly become the most commonly performed procedure (figure 1). However, in the paediatric age group, PK still outnumbers EK and ALK procedures (figure 2) with no increasing trend of EK that we see in adults. This is similar to a retrospective study by Harding *et al*[3] conducted in Eastern China on paediatric keratoplasties.

There are unique challenges in paediatric cornea transplantation compared with adults.[4–6] Preoperatively, a comprehensive evaluation of corneal pathology in children is frequently challenging due to difficulties in examination and diagnostic testing, often necessitating frequent examinations under anaesthesia. The timing of surgery is also crucial to minimise the risk of amblyopia.[7] Postoperatively, monitoring and examination are difficult with graft survival being poorer in children with higher rejection rates,[8] this is particularly so for repeat grafts.[5] It is also difficult for children to instil eyedrops independently and highly motivated care givers are important to ensure that postoperative eyedrop regime and follow-ups are adhered to.[3] Other ocular comorbidities such as cataract, glaucoma, macula hypoplasia, amblyopia and anterior segment dysgenesis may further limit visual rehabilitation.

ANTERIOR LAMELLAR KERATOPLASTY (ALK)

Leading indications for ALK include cornea scars, keratoconus, stromal dystrophies, superficial opacification such as previous cornea ulcer, congenital limbal dermoid, chemical injury, paediatric blepharokeratitis and mucopolysaccharidoses.[1 3 9–11] ALK rates are comparable between paediatric (40%) and adult (30%) groups in Singapore. When compared with PK, ALK offers a structurally stronger cornea, reduced long-term endothelial cell (EC) loss and lower risk of graft rejection.[7 10] Different techniques for ALK include hemi-ALK, automated lamellar

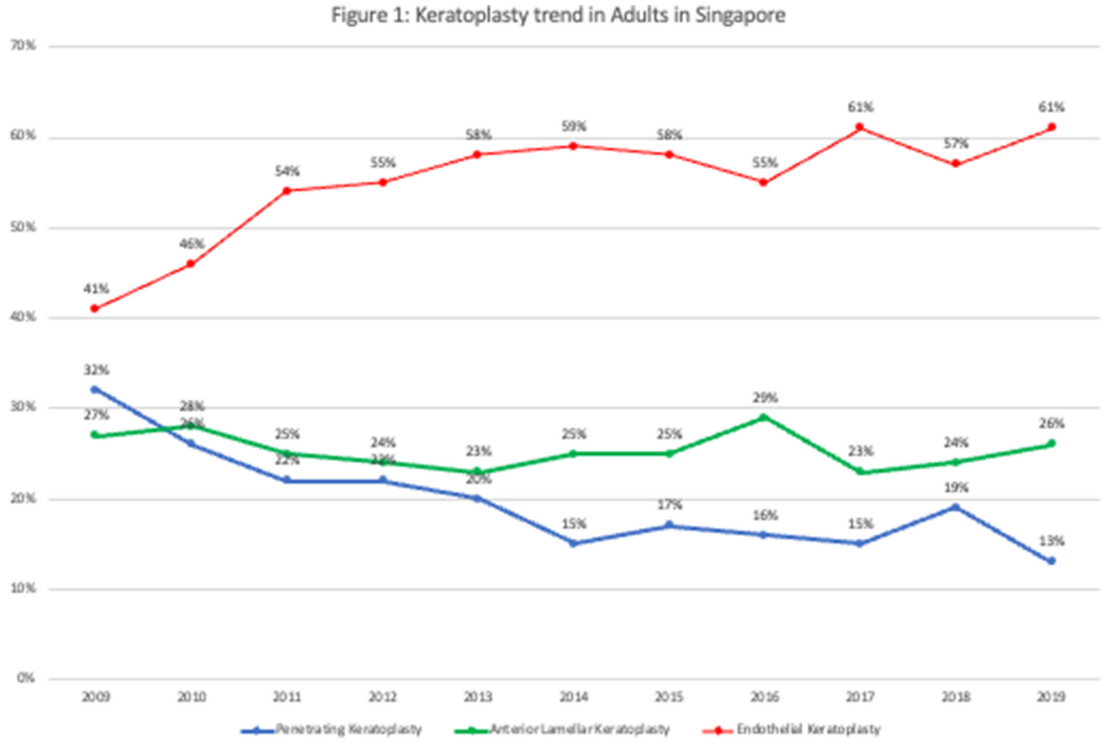

Figure 1 Trend of adult keratoplasty in Singapore. Among adults, endothelial keratoplasty has increasingly become the most commonly performed procedure.

therapeutic keratoplasty, femtosecond laser-assisted ALK and deep ALK (DALK).

Paediatric ALK presents distinct challenges compared with the adult population. Intraoperatively, surgeons encounter reduced scleral rigidity, higher vitreous pressure and increased susceptibility to buckling of host tissue during suture placement. Postoperatively, follow-up examination and suture removal might require repeated general anaesthesia in the operating theatre as children are less cooperative. There is also rapid healing of graft host junction and need for early suture removal.[3]

In the literature, there are limited case series reporting outcomes for paediatric ALK. The incidence of inadvertent intraoperative Descemet membrane (DM) perforation during DALK ranges from 9% to 40% depending on surgeon and technique.[12–14] While microperforations can

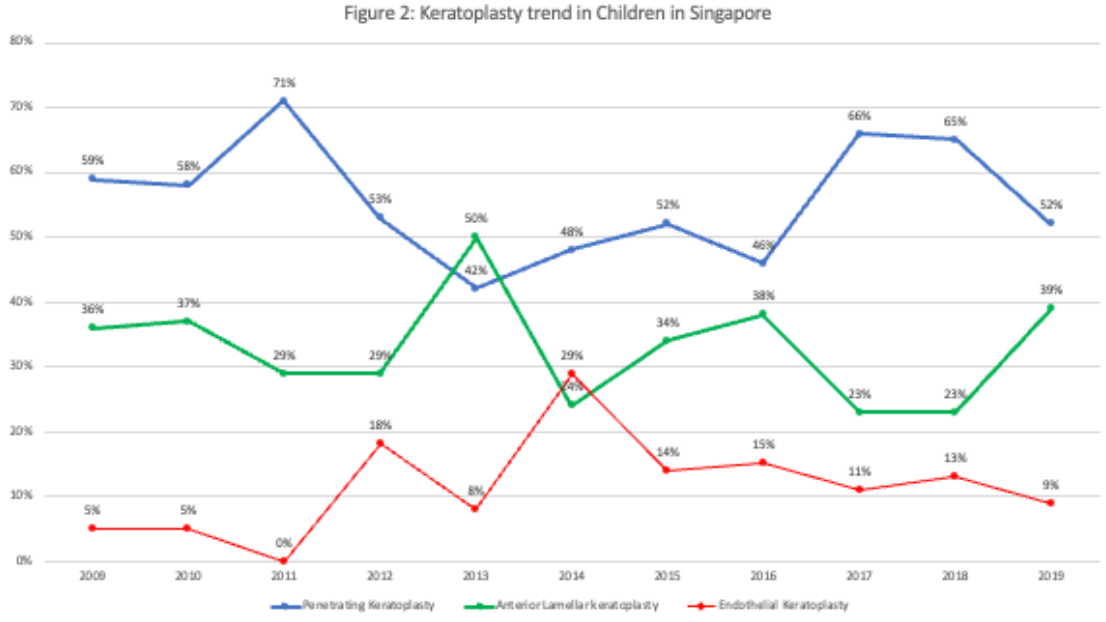

Figure 2 Trend of paediatric keratoplasty in Singapore. Among children, penetrating keratoplasty still outnumbers endothelial keratoplasty and anterior lamellar keratoplasty procedures.

be conservatively managed with intracameral air injection or heavy viscoelastic, large perforations may require conversion to PK.[12] Postoperatively, early complications encountered include DM detachment and elevated intraocular pressure (IOP) while late complications include graft failure, rejection and dehiscence.[15] Post-DALK DM detachment rates vary from 7.6% to 43%.[16 17] Most DM detachments were related to intraoperatively DM perforations and managed with intracameral air or gas injection. Incidence of high IOP post-DALK is lower than in PK and can be more effectively management with earlier cessation of steroid therapy.[18] In addition, children are more active and may be more prone to spontaneous or traumatic wound dehiscence during play.[19]

Visual outcome after DALK depends on the underlying indication for surgery and complications encountered.[9 20] Ashar *et al* reported a 69.23% graft clarity at 7.8 years follow-up in 26 eyes with anterior stromal opacity.[17] Meanwhile, Arora *et al* reported 90% clear DALK grafts at a follow-up period of 44.5 months in patients with advanced keratoconus without hydrops.[21] The rate of EC loss post paediatric DALK reported by Buzzonetti *et al*[7] in their experience was 11% within first 6 months followed by 1%–2% per year, which was lower compared with PK at 40% in the first year and 4.2% loss per year in the first 5–10 years. This is particular important for children who may need repeated cornea grafts.

ENDOTHELIAL KERATOPLASTY

EK is indicated for children with endothelial failure such as in congenital hereditary endothelial dystrophy (CHED), posterior polymorphous cornea dystrophy (PPCD), Peters anomaly, DM breaks post forceps delivery, cornea decompensation secondary to complicated intraocular surgery, traumatic aniridia and aphakia, buphthalmos and irreversible PK graft failure.[22 23] Two types of EK are commonly practiced—DSAEK and DMEK.

Paediatric DSAEK

Surgical considerations and complications in paediatric DSAEK

DSAEK in the paediatric population requires surgical modifications. Identifying and scoring of the DM in children is challenging due to its strong adhesions with the overlying stroma. Complications in this process, especially in infants, may lead to trauma to the posterior stromal fibres, necessitating a conversion to PK. In older children, the visibility of the DM intraoperatively can be enhanced through debridement of the epithelium, the use of an endoilluminator and staining of DM with trypan blue dye.[22 23] Alternative non-DM scoring methods in non-descemet stripping endothelial keratoplasty (nDSEK) have also proven successful in children with CHED.[23–25]

Donor graft insertion can also be performed through the push technique (using 40–60 taco fold), or the pull-in technique (using a Busin glide, Sheet's glide or Endoglide).[24 26–28] To minimise repeated iris prolapse due to positive vitreous pressure, employing the sheet's glide and suturing all ports before injecting air is effective for graft attachment.[23] Shifting incisions superiorly by 1 mm from conventional nasal and temporal placements are also helpful. Additional aids such as the anterior chamber maintainer, pilocarpine or sheet's guide help to prevent accidental intraoperative lens touch, which could lead to premature cataract formation. Yang *et al* recommended the use of an anchoring 10–0 prolene stitch tied to create a loop for pulling the donor lenticule inside the anterior chamber.[29] It has also been suggested that using donor tissue 0.5 mm smaller than the PK graft can decrease the risk of dislocation, particularly in cases where DSAEK is performed under a previously failed PK graft.[30 31]

Postoperatively, graft detachment rate after DSAEK in children may be as high as 21%.[32] Potential causes include a rough retrocorneal surface or retained DM. Furthermore, unlike adults, it is difficult to control eye rubbing and immediate postoperative supine posturing in children.[33] The incidence of graft detachment may be reduced through techniques like surface corneal massage, leaving 60%–70% air fill without inferior peripheral iridectomy (PI) or 80%–90% air fill with PI, venting incisions or discouraging eye rubbing with analgesia and strict eye shield.[22] Graft suturing should also be considered in younger and more active children. Reattachment of graft can usually be obtained with rebubbling, but this necessitates a repeat general anaesthesia for the child.

In figure 3, we demonstrate a case of DSAEK performed after a failed PK for a child with anterior segment dysgenesis. The PK was performed 3 years prior. At postoperative day 4, central stromal thickness (CST) was at 794 µm and reduced further to 581 µm with improved graft clarity in postoperative week 3. In postoperative month 2, CST stabilised at 480 um and he achieved a best-corrected visual acuity of 6/21 at postoperative month 48.

Outcomes of paediatric DSAEK

A significant factor for graft survival in DSAEK is EC loss. This has been reported to be from 19% to 53% in the literature with follow-up range from 0.9 to 3.4 years.[23 32 33] EC loss might be more pronounced in Asian eyes due to anatomical differences of smaller eyes with shallower AC and higher vitreous pressure. These factors contribute to greater difficulty in intraocular manipulations during surgery.[33]

Another common complication post-DSAEK is lenticular opacification and this may either be associated with underlying pathology or accelerated after surgical insult. The risk of cataract formation increases due to inadvertent lens touch, hypoxic damage from prolonged air tamponade during surgery, recurrent surgical interventions, postoperative inflammatory response and steroid use. Managing cataracts in post-DSAEK eyes is challenging as cataract extraction surgery may predispose to rejection and accelerate EC loss, eventually leading to graft failure.[34–37] Furthermore, the removal of the natural crystalline lens leads to loss of accommodation and compromise near vision, which is extremely important

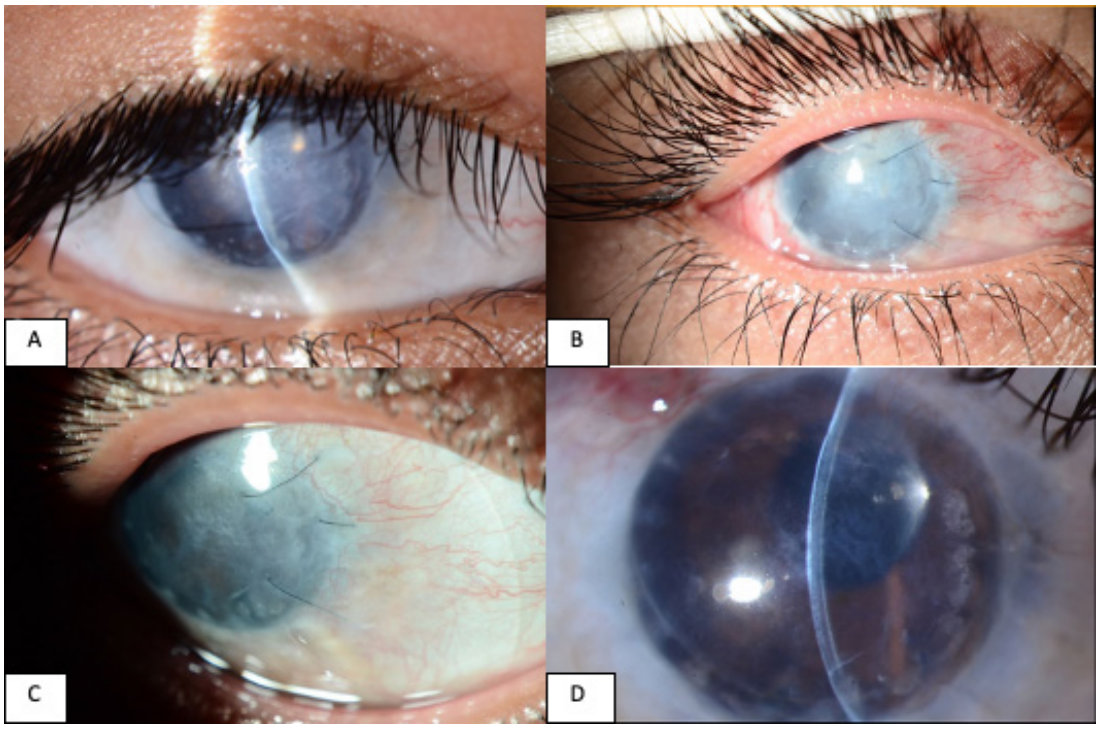

Figure 3 Clinical photo (A): right eye with a failed PK. Best corrected visual acuity at counting fingers closely. (B): Postoperative day 4 DSAEK under existing PK. Central stromal thickness was 794 µm. (C): Postoperative week 3 with central stromal thickness 581 µm. (D): Postoperative month 48 showing clear graft with visual acuity at 6/12. DSAEK, Descemet stripping automated endothelial keratoplasty; PK, penetrating keratoplasty.

for young children. Hence, removal of air tamponade immediately rapidly after 7–10 min and judicious use of corticosteroids may help delay the development of cataract.

Additional complications reported post-DSAEK include progressive anterior segment fibrosis, persistent stromal haze and donor-related abnormalities like irregular thickness, wrinkles and folds. Immunologic rejection is less frequently in DSAEK and may be reversed with intensive topical steroid therapy.[32] It is crucial to recognise that graft rejection in children may be diagnosed late as children are less forthcoming with visual symptoms and less cooperative with silt lamp examination.[32]

In literature, CHED is the most common indication for paediatric DSAEK.[25] Compared with traditional PK, DSAEK in CHED patients yields fewer postoperative complications and achieves good visual recovery with only mild residual haze.[25 30 31] Ramappa *et al* have reported graft survival rates of 92.7% at 1 year and 77.7% at 7 years in their experience with 167 eyes.[34] Following DSAEK surgery, cornea clearing may begin within 1 week and continue for 1 year. As cornea oedema clearing is seen faster in the younger age group, Yang *et al* thus suggested that infants may benefit from DSAEK more than older children.[29] However, despite favourable anatomical recovery, quantifying visual outcomes in children can be challenging due to the unreliability of refraction and subjective assessment in this age group.[38]

In the context of refraction, DSAEK typically results in a hyperopic shift and the average astigmatism induced by DSAEK wounds is reported to be less than 3D in children.[32] Occasional myopic shifts may be observed in children and is potentially due to poor vision associated with the initial disease or natural eyeball growth in the first 2 years of life.[38]

In summary, suboptimal visual gains following DSAEK may be attributed to factors such as increased corneal thickness, residual cornea haze, existing ocular comorbidities and underlying amblyopia. Despite its advantages, optical clarity achieved with DSAEK may not be as good as PK in young children due to interface irregularity. DSAEK might be more beneficial in eyes characterised by localised posterior opacity with minimal anterior stromal involvement or severe cornea oedema.[32]

Paediatric DMEK

Surgical considerations for paediatric DMEK

In figure 4, we present a case of DMEK performed on a child with cornea scarring due to PPCD. He successfully underwent a DMEK with the following intraoperative considerations. Cornea epithelium was first debrided to improve visibility. An inferior PI was performed to allow a postoperative large air bubble and prevent pupil block. A double-port anterior chamber maintainer was also used to maintain anterior chamber depth, mitigate the risk of lens touch and minimise excessive graft movement. As DM is more adherent in children, graft stripping was performed under viscoelastic instead of air. Stromal tags were removed with Utrata forceps and this was important for graft apposition and prevent graft dislocation.

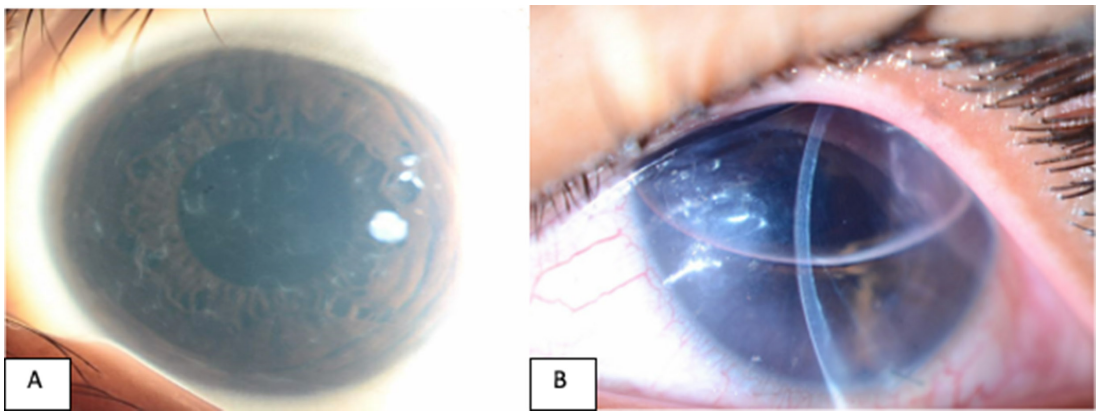

Figure 4 Clinical photos of child with PPCD. (A): Preoperative with best-corrected visual acuity of 6/30. (B): Postoperative day 1. PPCD, posterior polymorphous cornea dystrophy.

A modified donor insertion technique was employed with endothelium-in instead of endothelium-out. The endothelium-in technique was advantageous since it minimised shallowing of the anterior chamber and prevented lens injury. Minimal tapping on cornea for unscrolling also allowed for less vibration on the lens capsule to reduce lens opacification and fibrin formation.

Postoperatively, he was instructed to lie supine for as much as possible for a day and was started on intensive topical steroids of prednisolone forte 1% with antibiotic tobramycin 0.3% cover. On postoperative day 1, vision was at 6/120 and there was a clear, well-attached DMEK graft with 60% air bubble as shown in figure 4B. IOP was normal at 16 mm Hg. He continued to recover well and cornea clarity improved. At postoperative month 24, best-corrected vision was 6/6 with EC count at 1965cells/mm^2.

Outcomes of paediatric DMEK

DMEK is infrequently performed in the paediatric age group compared to DSAEK. The first reported case of paediatric DMEK was reported in 2014 by Gonnermann *et al*.[39] The patient was a 12-year old with cornea endothelial dysfunction in Kearns-Sayre syndrome. In the surgery, a central 9 mm desmetorhexis was performed under balanced salt solution after delineation with trypan blue dye. The graft was injected endothelial out followed by complete air fill for 30–40 min. Subsequently air–fluid exchange was performed to prevent pupillary block. Postoperatively, the child was instructed to lie supine for the first 24 hours. After 6 months, the central cornea thickness (CCT) of the child improved significantly from 837 um preoperatively to almost normal at 583 um. However, not all cases of DMEK's are successful. In one instance, DMEK for a 4-month-old infant with Posterior Polymorphous Cornea dystrophy resulted in graft dislocation on postoperative day 5.[38] An attempt to unfold the DMEK scroll with rebubbling was unsuccessful and a repeat DSAEK was required. In more recent literature, Srinivasan *et al*[40] performed three DM stripping and two non-DM stripping DMEKs and achieved success in 4 out of 5 eyes with 40% requiring rebubbling. A cohort study by Saad *et al*[41] reported rebubbling in 20% of 14 eyes with CHED and one graft failure. Wu *et al*[42] have also successfully performed bilateral DMEK in a 3-month-old infant with CHED and achieved improvement of visual acuity, nystagmus and cornea clarity. A case series of 11 eyes in six children under 8-year-old with cornea opacity due to CHED and congenital glaucoma who underwent DMEK also showed promising results.[43] Sutures were removed 1 week postoperatively and cornea oedema cleared in all eyes within 2 weeks postoperatively. Hence, visual stimulation therapy and amblyopia treatment could be started early. The study group achieved postoperative best-corrected vision ranging from 20/25 to 20/60 at follow-up period of 12 to 42 months. Separately, Ferguson *et al*[44] reported a case of successful DMEK in a 4-year old when intracameral tissue plasminogen activator was used to dissolve existing fibrin in the anterior chamber to aid in graft unscrolling.

Although DMEK in children is gradually gaining acceptance, potential postoperative complications such as DM detachment and the need for repeated general anaesthesia for rebubbling should be carefully considered before proceeding.

EK in Peters anomaly

Peters anomaly is the most common cause of congenital cornea opacity[45 46] and represents a group of diseases that result in cornea opacity with posterior cornea defect due to dysgenesis of the anterior segment during embryological development. Classifiable into three types, Peters anomaly type I manifests with central cornea opacity and iridocorneal adhesions, while type II involves central cornea opacity with cataracts or keratolenticular adhesions. Peters plus syndrome combines Peters anomaly with systemic disorders like short stature, developmental delay and cleft lip or palate. However, severity variation of cornea involvement exists within each classification. For instance, within type 1 Peters anomaly, the patient's cornea opacity can be peripheral, para-axial, central but small, central and large or diffuse. The type of Peters

anomaly might hence not be an accurate representation of visual impact of the patient. In addition, Peters anomaly is also associated with glaucoma and other lenticular abnormality which limits amblyopic visual development.

In the treatment of Peters Anomaly, Elbaz *et al*[47] proposed a disease phenotype-oriented management algorithm, which focused on the extent of cornea opacity regardless of specific Peters anomaly type. In their study involving 80 eyes from 54 patients, observation was recommended for mild disease with peripheral opacity, while small lesions (<3 mm) could be managed with pharmacological dilation or optical iridectomy. Lesions larger than 3 mm were considered suitable for PK.

The success rates following PK in Peters anomaly range from 22% to 83%. In a study by Chang *et al*,[48] among 166 eyes with Peters anomaly with 44 who had surgical interventions, final visual acuity in the mild and severe disease groups was 1.783±0.909 and 2.543±logMAR, respectively. In the same group of patients, 36% of eyes with mild disease had a visual acuity of 20/400 or better while 93% of eyes with severe disease had vision of counting fingers or worse, with 52% having no perception to light. Another study by Zaidman[49] reported a PK graft survival of 75% at 75 months in thirty eyes with type I Peters anomaly. Fifty per cent of these eyes required treatment for glaucoma and had an overall poorer prognosis. Reported long-term 10-year survival rates vary, with Yang *et al*[50] and Dolezal *et al*[51] reporting success rates of 35% and 34%, respectively. Meanwhile, the probability of a clear graft at 10 years found by Elbaz *et al*[52] was 74.2% and 38.9% for type I and type II, respectively.

Optical iridectomy or pupillary dilation is also effective for some children with Peters anomaly. In previous studies by Junemann *et al*[53] and Spierer *et al*,[54] patients who underwent optical iridectomy achieved vision of 1.0–1.4 logMar and an improvement in vision of 2.5 to 1.6 logMar, respectively. Cases with bilateral opacities also performed better than unilateral involvement.

Authors generally recommend that should surgical intervention be deemed required, it should be done in first year of life to avoid amblyopia.[6 48] Furthermore, graft clarity does not always translate to good visual outcome for patients due to the presence of amblyopia and coexisting ocular conditions. In particular, the prevalence of pre and post-operative glaucoma significantly impacts visual potential for children with Peters anomaly.[55]

Selective endothelium removal in Peters anomaly

In Peters anomaly, there is an absent or attenuated DM and endothelium, leading to localised haze resulting from endothelial dysfunction while the surrounding tissue remain unaffected. In response to any endothelial defect, the neighboring healthy endothelial cells undergo enlargement and migration to cover the affected area. There have been reports of spontaneous clearance of cornea opacity in patients with Peters anomaly without any surgical intervention. However, this process takes years, posing challenges in the context of amblyopia management.[56] Therefore, a

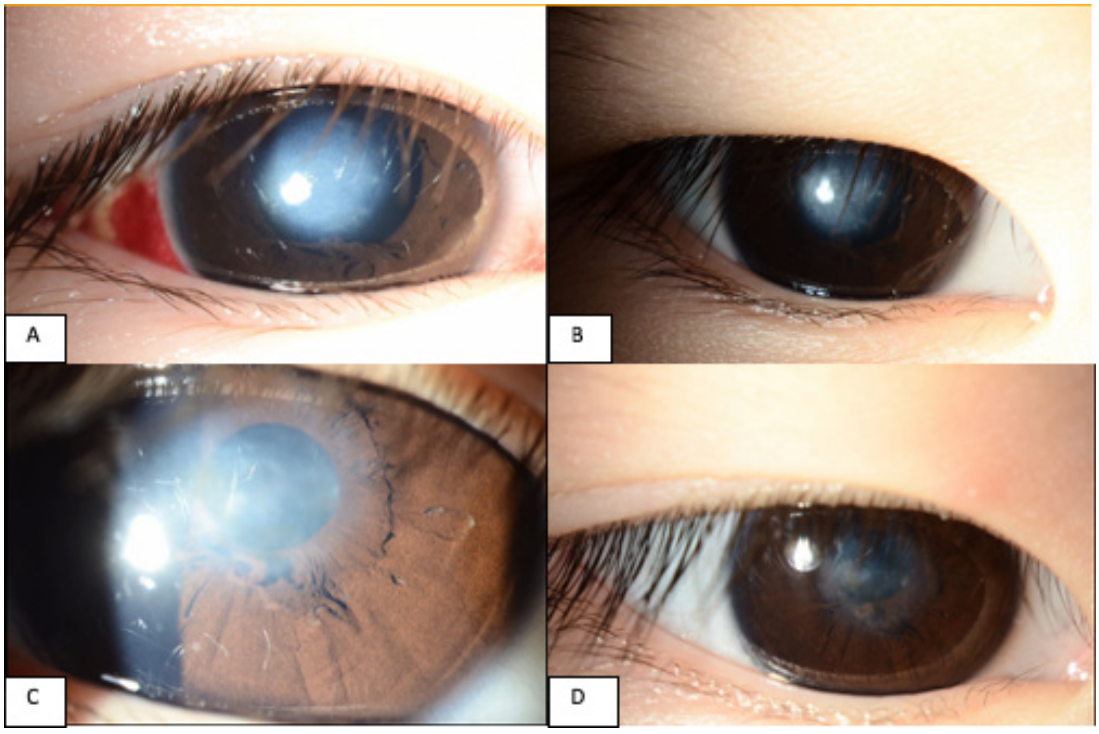

Figure 5 Clinical photos of child with Peters anomaly who underwent SER. (A): Preoperative. (B): Postoperative month 3. (C): Postoperative month 6. (D): Postoperative month 12 showing significant improvement in cornea opacity. SER, selective endothelium removal.

novel strategy, selective endothelium removal (SER), has been developed. SER focuses on adhesiolysis and selective removal of endothelium, to stimulate the centripetal migration of healthy peripheral endothelium, thereby establishing a functional monolayer and enhance corneal clarity. Soh *et al*[57] have shown the regenerative capability of the endothelium in cadaveric human corneas. Two types of wounds were induced: scratched corneas, leading to denuded endothelium while the DM remains intact, and peeled corneas, where both endothelium and DM were stripped. These corneas were cultivated in two different mediums: standard versus Rho-associated protein kinase inhibitor (ROCK) inhibited supplemented culture medium. The results revealed that corneal ECs preferentially migrated over scratched wounds compared with peeled wounds, emphasising the significance of an intact DM in cell migration. Additionally, endothelial migration decreased with age but increased with the presence of a ROCK inhibitor supplementation.[57] The study emphasised the importance of DM in endothelial wound healing, a notion supported by animal models as well.[58]

SER has been successfully performed in children. In figure 5, we demonstrate an example of SER on a 3-month old with type 1 Peters anomaly. During surgery, an anterior chamber maintainer was first inserted and clear cornea incision made. Iridocorneal adhesiolysis was done and a custom-made silicone soft tip was used to debride unhealthy endothelium with preservation of intact DM. Staining with trypan blue confirmed an endothelial defect and the absence of reflective ring on posterior cornea when air bubble was injected verified that the DM was still intact. Postoperatively, the child achieved favourable outcome of improved visual acuity and CCT at month 3, 6 and 12 at 20/130 CCT 528, 20/94 CCT 509, 20/30 CCT 465, respectively (figure 5). Amblyopic treatment was continued and patient was eventually weaned off topical eyedrops. There was a faint residual stromal scarring, which was expected to clear with time due to improved endothelial function. At the latest visit, visual acuity was 20/30 in both eyes.[59] Similar promising results were found in a case series published by our group when performed in three eyes with type 1 and one eye with type 2 Peters anomaly.[60] At 4–5 years follow-up, all eyes remain clear with no need for any ophthalmic eyedrops. Similarly, a study by Ramappa *et al*[61] which involved 34 eyes of 28 children with significant posterior cornea defect due to Peters anomaly also yielded positive results. In their protocol, SER was performed on its own or with additional procedures of optical iridectomy or lensectomy. Eleven eyes (32.4%) had significant clearing of cornea opacification by 3 months, 18 eyes (52.9%) had improvement of cornea clarity with functional vision and five eyes (14.7%) showed no improvement. Possible risk factors for failure noted were severe disease (p<0.0001), glaucoma (p=0.001) and additional interventions required (p=0.002). There were no sight-threatening complications encountered. This demonstrates the potential of SER to be used as an effective alternative treatment for selected patients with Peters anomaly.

FUTURE ADVANCES AND CONCLUSION

In conclusion, lamellar keratoplasty in children compared with adults presents unique surgical challenges and increased difficulties in examination and postoperative care. Nevertheless, children have the most to gain by new lamellar keratoplasty techniques with faster visual recovery, lower risk of rejection, fewer drops and importantly, earlier amblyopia treatment. Overcoming these technical challenges may establish lamellar keratoplasty as a viable alternative to PK and ensure that children do not miss out in the evolving lamellar revolution. In addition to advancements in surgical approaches for cornea endothelial dystrophies, there are promising developments in potential medical treatment for patients with SLC4A11 solute transport dysfunction autosomal recessive CHED.[62–64] SLC4A11 plays a crucial role in promoting adhesion to components of the DM and binding corneal EC.[65] Certain SLC4A11 gene mutation results in the production of misfolded SLC4A11 proteins that fail to be transported to the cell surface. A cell model study by Chiu *et al*[66] identified Glafenine, along with other non-steroidal anti-inflammatory drugs (NSAIDs), might have the ability to rescue trafficking defects in certain SLC4A11 mutants. Furthermore, ophthalmic NSAIDs like nepafenac or diclofenac could potentially increase cell surface level of SLC4A11 proteins as well.[67] Improved SLC4A11 protein levels in the DM might then improve cornea opacity for CHED patients without surgery. A randomised clinical trial assessing this hypothesis is currently underway. With continued progress in both surgical approaches and potential medical treatment, the future holds promise for re-establishing cornea clarity in the paediatric population.

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