The clinical outcomes of keratoplasty in irreversible corneal decompensation secondary to Axenfeld–Rieger syndrome

Ting Yu · Jing Hong · Ge-ge Xiao · Rong-mei Peng

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Abstract

Purpose To evaluate the clinical outcomes of penetrating keratoplasty (PK) and Descemet’s stripping automated endothelial keratoplasty (DSAEK) in eyes with irreversible corneal decompensation secondary to Axenfeld–Rieger syndrome (ARS).

Methods In this retrospective case series, a total of four eyes undergoing PK and seven eyes undergoing DSAEK, including one eye requiring one repeat DSAEK, between 2014 and 2021 were enrolled. Postoperative complications, graft survival, glaucoma treatment before and after keratoplasty, visual outcomes, and endothelial cell density were recorded.

Results The mean follow-up duration was 34.4 ± 16.8 months. Before keratoplasty, the mean BCVA was 2.0 ± 0.4 LogMAR, and the mean IOP was 21.7 ± 8.1 mmHg. A total of 63.6% of eyes (7/11) received glaucoma treatment, including five eyes with glaucoma surgeries. After keratoplasty, 27.3% of eyes (3/11) exhibited secondary graft failure. The mean BCVA reached a maximum of 0.7 ± 0.5 LogMAR at 8.9 ± 7.5 months, with no significant difference between the PK and DSAEK groups ($P_1 = 1.00$, $P_2 = 0.12$). Four eyes with previous glaucoma surgeries exhibited markedly high IOP. A total of 72.7% of eyes (8/11) required additional glaucoma treatments. The mean endothelial cell loss (ECL) rates at 1, 6, 12 and 24 months were 43%, 49%, 63% and 54%, respectively, with no significant difference between the PK and DSAEK groups ($P_1 = 0.64$, $P_2 = 1.00$, $P_3 = 0.57$, and $P_4 = 0.44$).

Conclusion Both PK and DSAEK can successfully treat corneal decompensation secondary to ARS, resulting in similar outcomes with regard to IOP control, BCVA and ECL. IOP control is essential for postoperative management, especially for eyes with previous glaucoma surgeries.

Keywords Corneal decompensation · Axenfeld–Rieger syndrome · Keratoplasty

Introduction

Axenfeld–Rieger syndrome (ARS) is a rare autosomal dominant disease considered part of the ocular anterior segment dysgenesis spectrum, with a prevalence estimated at 1 in 50,000–100,000 newborns [1]. The spectrum of ARS demonstrates locus heterogeneity with two major genes, forkhead box protein C1 (FOXC1, chromosome 6p25) and pituitary homeobox2 (PITX2, chromosome 4q25) [1, 2]. ARS is characterized by varying degrees of anterior segment dysgenesis, with or without craniofacial abnormalities and redundant periumbilical skin [2–5].
Major reported anterior segment features associated with ARS include iris stromal hypoplasia, iridocorneal adhesion, corectopia (distorted or displaced pupils), polycoria (extra holes in the iris), ectropion uveae and posterior embryotoxon (a prominent, anteriorly displaced Schwalbe’s ring near the temporal, posterior corneal limbus with a slit lamp) [4]. Other uncommon systemic anomalies include umbilical hernia, cardiovascular abnormalities and pituitary abnormalities [3].

Patients with ARS have an approximately 50% risk of developing glaucoma [2]. However, corneal abnormalities are uncommon in ARS [2, 3]. Keratoplasty is taken into account if irreversible corneal decompensation due to corneal endothelial cell loss causes pain and loss of visual acuity, which interfere with a patient’s normal activities. For many years, penetrating keratoplasty (PK) has been used for the surgical treatment of corneal endothelial diseases. The most common complications of PK are postoperative astigmatism and unpredictable anisometropia [6]. Descemet’s stripping automated endothelial keratoplasty (DSAEK) techniques are increasingly preferred over PK for endothelial dysfunction because of a less invasive process, minimal change in astigmatism, earlier visual rehabilitation, less frequent rejection, lack of suture–associated complications and better tectonic stability while maintaining comparable endothelial cell survival [7–10]. However, DSAEK is more challenging to perform than PK in eyes with ARS because the characteristics restrict the surgeon from working through a small incision to break the iridocorneal adhesion. In addition, iris abnormalities and shallow anterior chambers make graft manipulation and endothelial cell protection more difficult. Keratoplasty was once considered too risky and controversial for patients with ARS, especially pediatric patients, owing to the complicated anterior segment and high risk of secondary glaucoma. However, keratoplasty provides them an opportunity to regain the ability to live a normal life. Several publications have reported the glaucoma management of ARS, but there are very few studies about the outcomes of keratoplasty in patients with ARS [11, 12]. Whether PK or DSAEK is predominant in the treatment of irreversible corneal decompensation secondary to ARS remains to be elucidated.

The aim of this study was to describe the effect of keratoplasty on graft survival, intraocular pressure (IOP) control, visual acuity, and endothelial cell loss in eyes with irreversible corneal decompensation secondary to ARS and to compare these outcomes between PK and DSAEK.

Methods

In this retrospective, interventional consecutive case series, we included 11 eyes from seven patients who were clinically diagnosed with irreversible corneal decompensation secondary to ARS and treated with keratoplasty at the Ophthalmology Department of Peking University Third Hospital from January 2014 to January 2021. The study was conducted in compliance with the principles of the Declaration of Helsinki and approved by the Human Research Ethics Committee of Peking University Third Hospital. Informed consent to use images and data in this study was obtained from each participant or their guardian.

Patients were diagnosed according to the following inclusion criteria [3–5]: (1) bilateral congenital anterior segment dysgenesis, including iris abnormalities, such as iris stromal hypoplasia, corectopia, polycoria, ectropion uveae, iridocorneal adhesion or posterior embryotoxon; (2) corneal edema and/or opacity; with or without (3) systemic abnormalities, including midface dysmorphism, dental abnormalities, redundant periumbilical skin or other systemic defects.

Preoperative case records were reviewed for the following data: demographics (age at time of keratoplasty and sex), ocular histories (medical and surgical interventions), best-corrected visual acuity (BCVA) (LogMAR visual chart), IOP (Goldmann tonometer), slit–lamp findings, central corneal thickness (CCT) and anterior chamber depth (ACD) (anterior segment optical coherence tomography) (AS–OCT, Visante, Carl Zeiss Meditec, Dublin, CA, USA), morphological changes and endothelial cell density (ECD) in central endothelial cells (in vivo confocal microscopy) (IVCM, Heidelberg Retina Tomograph 3 with Rostock Cornea Module; Heidelberg Engineering, GmBH, Dossenheim, Germany) and ECD of the donor tissue (Specular microscope Group I, Class A) (HAI EB–3000 xyz, HAI laboratories, Inc., USA). For LogMAR values worse than 1.6, the following previously described scale was used: counting fingers, 2.0; hand motion, 2.3; light perception, 2.6; and no light perception, 2.9 [13].
Surgical technique

All keratoplasty operations were performed by a single surgeon (JH). In addition to their own or their guardians’ wishes, patients with severe edematous corneas or extremely shallow anterior chambers underwent PK, while the others underwent DSAEK. Referring to the standard procedures, PK (four grafts, three patients) and DSAEK (eight grafts, five patients) were performed to replace the full-thickness edematous cornea and the diseased corneal endothelium, respectively [14, 15].

Synechiolysis and special considerations for PK

After full-thickness corneal trephination, the iris adhered to the excised cornea was cut with microscissors. Iridocorneal adhesion was carefully broken with viscoelastic (Abbott Medical Optics, Abbott Park, Illinois, USA) or microscissors. Then, the donor tissue was transferred to the host and sutured with 10–0 Prolene sutures. To reduce the risk of peripheral anterior synechiae (PAS) and secondary glaucoma postoperatively, a 0.75–1.00 mm oversized donor cornea was sutured, which depended on each patient’s specific requirements.

Synechiolysis and special considerations for DSAEK

An epithelial trephine mark with a diameter of 7.5 or 8.0 mm was made. Viscoelastic from the paracentesis incision was required to break iridocorneal adhesion and maintain the anterior chamber. However, the iris that adhered to the cornea tightly was broken with the mental stab knife. A reverse Terry–Sinskey hook (Bausch and Lomb Surgical, St. Louis, MO, USA) was used to score the endothelium/DM. Then, a Terry Scraper (Bausch and Lomb Surgical) was used to smooth out the rough recipient bed, especially the periphery. Gentle pressure was applied to the inner cornea, taking care not to tear or disrupt corneal stromal fibers. To avoid postoperative PAS and angle obstruction, the 1.0-mm rim of endothelium/DM within the limbus was left behind. The donor tissue was prepared by a Moria automated lamellar therapeutic keratoplasty microkeratome and associated artificial anterior chamber (Moria Inc. Doylestown, PA, USA). A donor lenticule ranging from 120 to 150 μm in thickness was recommended. Removing viscoelastic, the donor lenticule was inserted into the anterior chamber with the suture pull–through insertion technique [14, 15] and unfolded in balanced salt solution (BSS, Alcon, Fort Worth, TX, USA). A lenticule–sized bubble was injected from the paracentesis incision, and the donor lenticule was positioned and centered with a roller. The air bubble was maintained for 10 min and then reduced to 75% volume in the anterior chamber. The patient remained supine for 4 h as required after DSAEK.

Postoperative management

Topical eye drops, including prednisolone acetate (1.0%, Allergan, Inc., Dublin, Ireland), levofloxacin (0.5%, Santen Co., Ishikawa, Japan) (patients aged 12 years or older) or tobramycin (0.3%, Alcon Laboratories, Inc., Fort Worth, TX) (patients younger than 12 years), and artificial tears were administered 4 times daily for the first week, with a gradual decrease as clinically indicated in the following 12 months. Then, a maintenance regimen of low–dose steroids was used from 12 months to 18–24 months after keratoplasty. Tobramycin and dexamethasone eye ointment (tobramycin 0.3% and dexamethasone 0.1%, Alcon Laboratories, Inc., Fort Worth, TX) was required every night for the first week after PK.

Cyclosporin (1%, North China Pharmaceutical Company, Ltd., Shijiazhuang, Hebei Province, China) (DSAEK) or tacrolimus (0.1%, Senju Pharmaceutical Co. Ltd., Japan) (PK) was applied 4 times daily from 1 week after keratoplasty, with a gradual decrease as clinically indicated in the following 18–24 months. All children were referred to a pediatric ophthalmologist for amblyopia treatment 1 month after keratoplasty.

Patients were routinely evaluated at 1, 3, 7 and 30 days, 3 months, 6 months and 12 months after keratoplasty and twice per year thereafter. More frequent reviews were performed as necessary. BCVA, IOP, corneal clarity and complications were recorded at each follow-up. IVCM for determining central ECD was performed at 1, 6 and 12 months and once per year thereafter. Graft rejection, primary graft failure and secondary graft failure were defined as described previously [16, 17]. The values were excluded from the following analysis in the presence of irreversible corneal decompensation and repeat keratoplasty.
Statistical analysis

The endothelial cell loss (ECL) rate was calculated by subtracting postoperative ECD from baseline donor ECD and then dividing by baseline donor ECD and multiplying by 100. The distribution of the data was assessed for normality via the Kolmogorov–Smirnov–Lilliefors test. Data are presented as the mean ± standard deviation. The data with a normal distribution were estimated using a t test. Analysis for data with nonnormal distributions was performed using the Wilcoxon Mann–Whitney or Wilcoxon signed rank test as appropriate. Categorical variables were compared using Chi-square/Fisher’s exact test. The potential association between the 6-month ECL rate and the 12-month ECL rate and previous glaucoma surgeries, baseline IOP, ACD before keratoplasty, type of keratoplasty, and additional glaucoma surgeries after keratoplasty was assessed by analysis of variance. A two–sided P value < 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS statistics, version 24.0 (SPSS, Inc., Chicago, IL, USA).

Results

Eleven eyes of seven patients were included in the study. Family history was positive for ARS in one patient (Patient 6). Two patients underwent genetic counseling, and genomic DNA from the patients’ blood samples was PCR–amplified and screened for mutations in PITX2 c.253 A > G (Patient 3) and PITX2 c. 286 C > T (Q96X) (Patient 6). Physical examinations revealed craniofacial abnormalities in all patients and redundant periumbilical skin in four patients. The mean age was 16.7 ± 12.6 years (range, 6.3–39.8 years) at the time of first keratoplasty, and five (71.4%) were male. The mean follow-up duration was 34.4 ± 16.8 months (range, 11–61 months). There was no significant difference between the PK group (n = 4, 36.4%) and DSAEK group (n = 7, 63.6%) (P = 0.13) (Table 1).

Before keratoplasty, the mean BCVA was 2.0 ± 0.4 LogMAR (range, 1.1–2.6 LogMAR), and two eyes (18.2%) had BCVA ≥ 1.3 LogMAR (Snellen equivalent, 20/400). The mean IOP was 21.7 ± 8.1 mmHg (range, 12–36 mmHg). There was no significant difference between the PK and DSAEK groups in the BCVA ≥ 1.3 LogMAR and IOP (P1 = 0.49, P2 = 0.13) (Table 1). One PK eye and four DSAEK eyes showed elevated IOP (> 21 mmHg). One of four PK eyes

| Table 1 | Comparison of baseline characteristics and clinical outcomes between PK and DSAEK eyes |
|-------------------|---------------------------------|-----------------|---|
| **Baseline characteristics** | **PK (four eyes of three patients)** | **DSAEK (seven eyes of five patients)** | **P value** |
| Age at the time of first keratoplasty, year (range) | 11.5 ± 7.0 (6.3–21.4) | 19.6 ± 14.5 (6.8–39.8) | 0.35 |
| Male sex, n (%) | 2 (66.7%) | 4 (80.0%) | 1.00 |
| Duration of follow-up, year (range) | 44.5 ± 14.8 (31–61) | 28.6 ± 16.0 (11–47) | 0.13 |
| Mean BCVA, LogMAR | 2.1 ± 0.2 | 2.0 ± 0.5 | 1.00 |
| BCVA ≥ 1.3 LogMAR before keratoplasty, n (%) | 0 (0) | 2 (28.6%) | 0.49 |
| IOP before keratoplasty, mmHg | 17.0 ± 6.3 | 24.3 ± 8.2 | 0.13 |
| Elevated IOP (> 21 mmHg), n (%) | 1 (25.0%) | 4 (57.1%) | 0.55 |
| Glaucoma treatment before keratoplasty, n (%) | 1 (25.0%) | 6 (85.7%) | 0.09 |
| **Clinical outcomes after keratoplasty** | | | |
| Primary graft survival, n (%) | 3 (75.0%) | 5 (71.4%) | 1.00 |
| Additional glaucoma treatment, n (%) | 2 (50.0%) | 6 (85.7%) | 0.49 |
| Maximum mean BCVA, LogMAR | 0.7 ± 0.5 | 0.7 ± 0.6 | 1.00 |
| Maximum BCVA ≥ 1.3 LogMAR after keratoplasty, n (%) | 4 (100%) | 6 (85.7%) | 1.00 |
| Time approaching the maximum BCVA, months | 13.5 ± 9.0 | 6.3 ± 5.7 | 0.12 |

*Using Fisher’s exact test for categorical variables and Wilcoxon Mann–Whitney test for continuous variables
(25.0%) required topical glaucoma medications and surgeries; however, six of seven DSAEK eyes (85.7%) required topical glaucoma medications: two of these (33.3%) were on topical medications alone, while four (66.7%) had previous glaucoma surgeries. One eye with lens anterior dislocation underwent combined cataract extraction–synechiolysis–gonioplasty–anterior vitrectomy–posterior chamber intraocular lens (PCIOL) implantation, followed by an elevated IOP (Patient 3, right eye) (Table 2).

Additional surgical procedures during keratoplasty included synechiolysis (n=11), phacoemulsification with PCIOL implantation (n=2).

Intraoperative and postoperative complications

All surgical interventions were successful, and no intraoperative complications were noted. There was no immediate markedly elevated IOP, interface fluid or graft detachment. Mean PAS involved 5 clock hours without progressive manifestations.

Graft survival

Eight of 11 primary grafts (72.7%) survived during the follow-up period (Table 1). Because of secondary endothelial failure, one PK graft failed at 21 months, and two DSAEK grafts failed at 24 and 45 months, respectively (Table 2). One eye received repeat DSAEK (patient 4, left eye) (shown in Fig. 1).

Additional glaucoma treatment after keratoplasty

In the PK group, two of four eyes (50.0%) exhibited high IOP and received additional glaucoma therapy after keratoplasty: one eye without glaucoma history was on topical medications alone, while repeat glaucoma surgeries were performed for another eye with glaucoma history (Table 2). In the DSAEK group, of these six eyes with a history of glaucoma, five eyes (83.3%) required additional glaucoma treatment after keratoplasty; three were on topical medications alone, and two required glaucoma surgeries. One eye without a history of glaucoma required topical medications after keratoplasty (Table 2).

In general, four eyes exhibited markedly high IOP postoperatively and had previous glaucoma surgeries. Eight of 11 eyes (72.7%) received additional glaucoma treatment after keratoplasty: two (50.0%) in the PK group and six (85.7%) in the DSAEK group (P=0.49). Of these eight eyes, one PK eye (25.0%) and two DSAEK eyes (28.6%) required glaucoma surgeries. All three eyes underwent glaucoma surgeries before keratoplasty.

Visual outcomes

After keratoplasty, the mean BCVA reached a maximum of 0.7±0.5 LogMAR (range, 0.2–2.0 LogMAR) at 8.9±7.5 months. Ten eyes (90.9%) had BCVA≥1.3 LogMAR, and four eyes (36.4%) had BCVA≥0.3 LogMAR (Snellen equivalent, 20/40). The difference between the PK and DSAEK groups in the percentage of maximum BCVA≥1.3 LogMAR and the time approaching the maximum BCVA showed no significant difference (P1=1.00, P2=0.12) (Table 1).

ECD and ECL

Table 3 and Fig. 2 show the outcomes for ECD and ECL rate in the PK group and DSAEK group. The ECD values of donor tissues in the PK and DSAEK groups were not significantly different (P=0.155). Compared with the ECD of donor tissues, the ECL rate during PK and DSAEK was not significant at 1 month (P1=0.18, P2=0.07). There was no significant difference between the PK and DSAEK groups in the ECL rate at 1, 6, 12 and 24 months (P1=0.64, P2=1.00, P3=0.57, and P4=0.44).

The 6-month ECL rate and 12-month ECL rate, which were detectable for all 11 eyes, were not significantly correlated with previous glaucoma surgeries (P1=0.73, P2=0.46), baseline IOP (P1=0.71, P2=0.19), ACD before keratoplasty (P1=0.43, P3=0.67), type of keratoplasty (P1=1.00, P2=0.60), or additional glaucoma surgeries after keratoplasty (P1=0.99, P2=0.96).

Discussion

The prognosis for corneal grafts in ARS is not established due to a lack of published data [11, 12]. In the current study, we report the clinical outcomes of keratoplasty in 11 consecutive eyes with irreversible corneal decompensation secondary to ARS after a mean 3-year follow-up duration.
| No. | Age (year)/sex | Eye | Ocular abnormalities | Procedure (graft size) | BCVA (LogMAR) | IOP control | Postop CDR (after cleared graft) | Time to failure (mo) | FU (mo) |
|-----|----------------|-----|---------------------|-----------------------|---------------|-------------|---------------------------------|---------------------|--------|
| 1   | 6/F            | OD  | Cornea: edema + opaque (central) | PK-SL (7.25 mm)       | 2.0           | 0.3         | No                              | 0.3                 | 61     |
|     |                |     | Corneal diameter: 10.25 mm |                       |               |             |                                 |                     |        |
|     |                |     | Posterior embryotoxon: (-) |                       |               |             |                                 |                     |        |
|     |                |     | CCT: 1.22 mm |                       |               |             |                                 |                     |        |
|     |                |     | Iris: corectopia, IH, AS |                       |               |             |                                 |                     |        |
|     |                |     | ACD: 0.44 mm |                       |               |             |                                 |                     |        |
|     |                |     | Comorbidities: (-) |                       |               |             |                                 |                     |        |
|     |                |     | MEC: ND |                       |               |             |                                 |                     |        |
|     | OS  | Cornea: edema + opaque (central) | PK-SL (7.5 mm)       | 2.0           | 0.2         | 12 (Nil) | Yes; raised at 16 mo, controlled on 2 GM | 0.3                 | 53     |
|     |                |     | Corneal diameter: 10.5 mm |                       |               |             |                                 |                     |        |
|     |                |     | Posterior embryotoxon: (-) |                       |               |             |                                 |                     |        |
|     |                |     | CCT: 0.82 mm |                       |               |             |                                 |                     |        |
|     |                |     | Iris: corectopia, IH, AS |                       |               |             |                                 |                     |        |
|     |                |     | ACD: 0.55 mm |                       |               |             |                                 |                     |        |
|     |                |     | Comorbidities: (-) |                       |               |             |                                 |                     |        |
|     |                |     | MEC: ND |                       |               |             |                                 |                     |        |
| 2   | 7/M            |      | Cornea: edema + ulcer + opaque (diffuse) | PK-SL (7.0 mm)       | 2.3           | 1.0         | 19 (Nil) | No                              | 0.3                 | 31     |
|     |                |     | Corneal diameter: 10.0 mm |                       |               |             |                                 |                     |        |
|     |                |     | Posterior embryotoxon: ND |                       |               |             |                                 |                     |        |
|     |                |     | CCT: 1.44 mm |                       |               |             |                                 |                     |        |
|     |                |     | Iris: corectopia, polycoria, IH, AS |                       |               |             |                                 |                     |        |
|     |                |     | ACD: 1.48 mm |                       |               |             |                                 |                     |        |
| No. | Age (year)/sex | Eye | Ocular abnormalities | Procedure (graft size) | BCVA (LogMAR) | IOP control | Postop CDR (after cleared graft) | Time to failure (mo) | FU (mo) |
|-----|----------------|-----|----------------------|------------------------|---------------|-------------|---------------------------------|---------------------|--------|
| 3   | 11/M           | OD  | Cornea: edema + opaque (diffuse) | PK-SL (9.25 mm)        | 2.0 | 1.1 | 25 (2; CPC×2+GDD) | Yes; raised at 1 mo, controlled on CPC+GDD+combined CLASS-trabeculectomy–trabeculotomy at 14 mo | 0.8 | 21 | 33 |
|     |                |     |                      |                        |               |             |                                 |                     |        |

Corneal diameter: 11.5 mm
Posterior embryotoxon: (+)
CCT: 1.32 mm
Iris: corectopia, polycoria, IH, AS
ACD: 2.92 mm
Comorbidities: glaucoma
MEC: ND

Corneal diameter: 8.5 mm
Posterior embryotoxon: (+)
CCT: 1.03 mm
Iris: corectopia, IH, AS
ACD: 1.88 mm
Comorbidities: glaucoma

MEC: ND
**Table 2 (continued)**

| No. | Age (year)/sex | Eye | Ocular abnormalities | Procedure (graft size) | BCVA (LogMAR) | IOP control | Postop CDR (after cleared graft) | Time to failure (mo) | FU (mo) |
|-----|----------------|-----|----------------------|------------------------|---------------|-------------|--------------------------------|---------------------|--------|
|     |                |     |                      |                        | Baseline      | Postop max  | Baseline (No. of GM + GS)      |                     |        |
|     |                |     |                      |                        | Postop        | normal      | additional GM + GS             |                     |        |
| 4   | 7/M            | OD  | Cornea: edema + opaque (peripheral) | DSAEK-SL (7.0 mm)     | 1.6           | 0.5         | 13 (1)                          | Yes, raised at 1 mo, controlled on 2 GM | 0.4     | –      | 41     |
|     |                |     | Corneal diameter: 9.0 mm |                        |               |             |                                 |                     |        |
|     |                |     | Posterior embryotoxon: (+) |                        |               |             |                                 |                     |        |
|     |                |     | CCT: 0.88 mm          |                        |               |             |                                 |                     |        |
|     |                |     | Iris: corectopia, polycoria, IH, AS |                |               |             |                                 |                     |        |
|     |                |     | ACD: 1.07 mm          |                        |               |             |                                 |                     |        |
|     |                |     | Comorbidities: (-)    |                        |               |             |                                 |                     |        |
|     |                |     | MEC: irregular hexagonal ECs |                        |               |             |                                 |                     |        |
|     |                | OS  | Cornea: edema + opaque (peripheral) | 1. DSAEK-SL (7.0 mm) | 2.0           | 0.2         | 20 (Nil)                        | Yes, raised at 1 mo, controlled on 2 GM | 0.4     | 24     | 38     |
|     |                |     | Corneal diameter: 9.0 mm |                        |               |             |                                 |                     |        |
|     |                |     | Posterior embryotoxon: (-) |                        |               |             |                                 |                     |        |
|     |                |     | CCT: 0.94 mm          |                        |               |             |                                 |                     |        |
|     |                |     | Iris: corectopia, IH, AS | 2. DSAEK-SL (7.0 mm) | 1.1           | 0.4         | 16 (2)                         | No                  | 0.4     | –      | 9      |
|     |                |     | ACD: 1.33 mm          |                        |               |             |                                 |                     |        |
|     |                |     | Comorbidities: (-)    |                        |               |             |                                 |                     |        |
|     |                |     | MEC: irregular hexagonal ECs |                        |               |             |                                 |                     |        |
|     |                |     |                         |                        |               |             |                                 |                     |        |

MEC: ND (regular hexagonal ECs with bright nuclei were detected before corneal edema)

Corneal diameter: 9.0 mm

Posterior embryotoxon: (+)

CCT: 0.88 mm

Iris: corectopia, polycoria, IH, AS

ACD: 1.07 mm

Comorbidities: (-)

MEC: irregular hexagonal ECs

47 total
Table 2 (continued)

| No. | Age (year)/Sex | Eye | Ocular Abnormalities | Procedure (graft size) | BCVA (LogMAR) | IOP Control | Postop CDR (after cleared graft) | Time to failure (mo) |
|-----|---------------|-----|----------------------|-----------------------|---------------|-------------|----------------------------------|---------------------|
|     |               |     |                      |                       | Baseline | Postop maximum | Baseline (No. of GM + GS) |           |                          |                     |
| 5   | 21/M          | OS  | Cornea: edema + opaque (peripheral) + pannus | DSAEK-SL-Phaco-PCIOL (7.5 mm) | 2.6      | 2.0           | 17 (trabeculotomy) | Yes; raised at 2 mo, poorly controlled with 3 GM + PCIOL explantation-AV + CPC | 0.8               | –                  | 15                 |

Corneal diameter: 9.5 mm
Posterior embryotoxon: (+)
CCT: 0.73 mm
Iris: corectopia, polycoria, IH, AS, EU
ACD: 1.56 mm
Comorbidities: glaucoma, cataract
MEC: ND

6   | 40/F          | OD  | Cornea: edema + opaque (peripheral) + pannus | DSAEK-SL-Phaco-PCIOL (7.5 mm) | 2.0      | 0.4           | 30 (1; CPC × 2) | Yes; controlled on 3 GM + CPC + GDD at 33 mo | 0.9               | 45                 | 45                 |

Corneal diameter: 9.5 mm
Posterior embryotoxon: (+)
CCT: 0.77 mm
Iris: corectopia, polycoria, IH, AS, EU
ACD: 1.84 mm
Comorbidities: glaucoma, cataract, high myopia
MEC: ND
Table 2 (continued)

| No. | Age (year)/sex | Eye | Ocular abnormalities | Procedure (graft size) | BCVA (LogMAR) | IOP control | Time to failure (mo) | FU (mo) |
|-----|----------------|-----|----------------------|------------------------|---------------|--------------|---------------------|--------|
|     |                |     |                      |                        | Baseline      | Postop max.   |                     |        |
|     |                |     |                      |                        | Postop         |              |                     |        |
|     |                |     |                      |                        | 30 (GDD)      |              |                     |        |
|     |                |     |                      |                        | Yes, controlled on | Postop CDR   |                     |        |
|     |                |     |                      |                        | 2 GM          |              |                     |        |
|     |                |     |                      |                        | 0.6           |              |                     |        |
|     |                |     |                      |                        | –             |              |                     |        |
| 7   | 32/M OD        |     | Cornea: edema + opaque (peripheral) | DSAEK-SL (8.0 mm) | 2.3           | 0.5          | –                   | 11     |
|     |                |     | Corneal diameter: 10.0 mm |                        |               |              |                     |        |
|     |                |     | Posterior embryotoxon: (+) |                        |               |              |                     |        |
|     |                |     | CCT: 0.95 mm |                        |               |              |                     |        |
|     |                |     | Iris: corectopia, IH, AS |                        |               |              |                     |        |
|     |                |     | ACD: 2.59 mm |                        |               |              |                     |        |
|     |                |     | Comorbidities: glaucoma |                        |               |              |                     |        |
|     |                |     | MEC: ND (regular hexagonal ECs with bright nuclei were detected before corneal edema) | | | | | |
| OS  |                |     | Cornea: edema + opaque (central) | DSAEK–SL (8.0 mm) | 2.3           | 0.8          | –                   | 12     |
|     |                |     | Corneal diameter: 10.0 mm |                        |               |              |                     |        |
|     |                |     | Posterior embryotoxon: (-) |                        |               |              |                     |        |
|     |                |     | CCT: 1.09 mm |                        |               |              |                     |        |
|     |                |     | Iris: corectopia, IH, AS |                        |               |              |                     |        |
|     |                |     | ACD: 1.77 mm |                        |               |              |                     |        |
|     |                |     | Comorbidities: glaucoma |                        |               |              |                     |        |
|     |                |     | MEC: ND |                        |               |              |                     |        |

No, patient number; y, years; BCVA, best-corrected visual acuity; postop, postoperative; IOP, intraocular pressure; GM, glaucoma medications; GS, glaucoma surgeries; CDR, cup disc ratio; mo, months; FU, follow-up; M, male; F, female; OD, right eye; OS, left eye; CCT, central corneal thickness; ACD, anterior chamber depth; MEC, morphological changes in endothelial cells; IH, iris stromal hypoplasia; AS, anterior synechiae of the iris; EU, ectropion uveae; ND, not detectable; EC, endothelial cells; PK, penetrating keratoplasty; DSAEK, Descemet’s stripping automated endothelial keratoplasty; SL, synchondrosynthesis; Phaco, phacoemulsification; PCIOL, posterior chamber intraocular lens; CPC, cyclophotocoagulation; GDD, glaucoma drainage devices; CLASS, CO2 laser-assisted sclerectomy surgery; NR, needle revision of failed filtering bleb; AV, anterior vitrectomy. CCT and ACD were measured with AS-OCT; MEC were measured with IVCM.
Previously, patients with ARS were considered unsuitable for keratoplasty [18], although corneal decompensation secondary to ARS deprived them of the ability to normal life and work. However, there was no other effective treatment to release these patients from persistent pain and poor vision. Moreover, glaucoma might still be the greatest problem throughout their lifetime even without keratoplasty. Keratoplasty gave them an opportunity for restoring vision and hope of life. Therefore, they accepted keratoplasty for complaints related to great pain and vison loss.

The clinical outcomes in this series were encouraging. Both PK and DSAEK can successfully treat corneal dysfunction secondary to ARS, with a primary graft survival rate of 72.7% (8/11) at a 3-year follow-up. The graft survival was similar to results in a previous study on pediatric DSAEK [19]. Lacking published clinical outcomes of keratoplasty for the treatment of ARS, the surgical outcomes in our series were compared with those in iridocorneal endothelial (ICE) syndrome, which shares similar anterior segment manifestations with ARS and has an approximately 50% risk of developing glaucoma [20].

Table 3  Endothelial cell density and endothelial cell loss after keratoplasty

| Baseline | Follow-up visit |
|----------|-----------------|
|          | 1 Month | 6 Months | 12 Months | 24 Months |
| ECD (cells/mm²) | 3274 ± 490 | 1807 ± 634 | 1685 ± 766 | 1233 ± 591 | 1422 ± 467 |
| PK       | 2936 ± 466 | 1364 ± 93  | 1718 ± 1086 | 1152 ± 576 | 1575 ± 404 |
| DSAEK    | 3467 ± 414 | 2028 ± 686 | 1666 ± 622 | 1279 ± 705 | 1193 ± 1026 |
| ECL rate (%) | –  | 43 ± 15  | 49 ± 23  | 63 ± 16  | 54 ± 20  |
| PK       | –  | 47 ± 13  | 42 ± 35  | 60 ± 19  | 45 ± 14  |
| DSAEK    | –  | 41 ± 17  | 52 ± 17  | 64 ± 16  | 67 ± 25  |

ECD endothelial cell density, ECL endothelial cell loss, PK penetrating keratoplasty, DSAEK Descemet’s stripping automated endothelial keratoplasty Postoperative data were available for six eyes (five eyes from children) at 1 month, 11 eyes at 6 months, 12 months and five eyes (four eyes from children) at 24 months (in vivo confocal microscopy data were available for two PK eyes and four DSAEK eyes at 1 month, three PK eyes and two DSAEK eyes at 24 months)
Fig. 2 Median endothelial cell density (ECD) and median endothelial cell loss (ECL) rate for surviving grafts over time after keratoplasty

Table 4 Clinical outcomes of keratoplasty in eyes with ICE syndrome in reported major studies

| Study       | No. of eyes | Procedure | Mean follow-up | Graft survival | BCVA ≥ 20/40 | ECL 6 mo | ECL 12 mo | ECL 24 mo |
|-------------|-------------|-----------|----------------|----------------|--------------|---------|-----------|-----------|
| Mohamed [21]| 52 eyes     | EK        | 2.4 year       | 73.1%          | –            | 28%     | 37.9%     | 56.9%     |
| Rotenberg [22]| 86 eyes   | PK-58 eye-sEK-28 eyes | 5 year       | PK-64.3% (16) EK-66.8% (26) (Kaplan-Meier) | – | – | – | – |
| Ao [17]     | 20 grafts in 18 eyes | EK | 19.0±8.6 mo | 45%            | –            | 52.3% | 58.1%     | 69.3%     |
| Fajgenbaum [23]| 9 grafts in 4 eyes of 4 patients | EK | 55 mo | 25% (initial) | – | 78% | 80% | 83% |
| Quek [24]   | 29 eyes     | PK-17 eye-sEK-12 eyes | PK-7.0±4.9 yEK-4.0±2.6 y | PK-41%EK-33% | – | – | – | – |
| Chaurasia [25]| 8 eyes     | EK        | 12.5 mo       | 100%           | 87.5%        | – | – | – |
| Alvim [26]  | 14 patients | PK        | 58 mo         | 50% (initial)  | 21%          | – | – | – |
| Chang [27]  | 12 eyes     | PK        | 30 mo         | 83%            | 75%          | 13% | 17% | – |
| Buxton [28] | 5 patients  | PK        | 2.7 y         | 100%           | 100%         | – | – | – |
| Crawford [29]| 9 patients | PK        | 43 mo         | 100%           | –            | – | – | – |

ICE syndrome Iridocorneal endothelial syndrome, BCVA best–corrected visual acuity, ECL endothelial cell loss, mo months, y years, PK penetrating keratoplasty, EK endothelial keratoplasty

(Table 4). The graft survival rate in our study was favorable. Unlike the progression of synechiae after keratoplasty in ICE syndrome [29, 30], PAS showed no progressive manifestations in our series.

In the current study, 72.7% of eyes (8/11) required additional glaucoma treatment, which was higher than that in ICE syndrome conducted by a multicenter study [24]. This multicenter study including 17 PK eyes and 12 DSAEK eyes with ICE syndrome reported that 37.9% of eyes received glaucoma therapy after keratoplasty. The higher baseline IOP (21.7 ± 8.1 mmHg in our series vs. 14.7 ± 3.9 mmHg in the multicenter),
higher morbidity of glaucoma (63.6% in our series vs. 55.2% in the multicenter) and biometrically shallow anterior chamber in Asian eyes might be responsible for the higher rate of IOP elevation after keratoplasty in our series. In our study, the IOP in eyes with previous glaucoma surgeries was more difficult to control after keratoplasty. Of the eight eyes that required additional glaucoma therapy, three eyes showed mildly elevated IOP postoperatively, which was considered to be associated with the long-term use of topical corticosteroids; however, all four eyes with dramatically high IOP postoperatively had previous glaucoma surgeries.

The maximum BCVA in our series was similar to that reported in our previous study with ICE syndrome (0.57 LogMAR) but poorer than those in other previous studies (0.4–0.0 LogMAR) [23, 25, 30]. The difference in visual outcomes among these studies might be attributed to amblyopia and a higher morbidity of glaucoma in the current series and our previous study (63.6% and 65.0%) [17]. In our study, DSAEK eyes did not show better BCVA than PK eyes due to the higher morbidity of glaucoma. Although the DSAEK group reached a maximum BCVA more quickly than the PK group (6.3 months vs. 13.5 months), the difference did not reach statistical significance due to the small sample size. Four of seven (57.1%) DSAEK eyes underwent keratoplasty in adulthood when irreversible amblyopia had formed. In contrast, BCVA improved over time during the follow-up period in the PK group because all PK patients were children who accepted standard amblyopia treatment before keratoplasty, which contributed to their BCVA sequential improvement. Thus, this result might not be sufficient to indicate that DSAEK allows more rapid visual recovery than PK.

The decrease in postoperative ECD was prominent at the 1-month review in both PK and DSAEK, which is consistent with previous studies [17, 31, 32]. The complicated anterior segment in eyes with ARS leads to great difficulty in graft manipulation and increased perioperative inflammation, which is an important reason for the increased perioperative ECL [16, 23, 30]. In our study, the rate of ECL is higher in DSAEK group. We considered the progressive ECL in DSAEK group was attributed to a shallower anterior chamber after inserting a lenticule over 100 μm.

The study is limited by its retrospective nature and small sample size, primarily due to the rarity of irreversible corneal decompensation secondary to ARS. Although it is the largest series reported for both PK and DSAEK, the long-term clinical outcomes of keratoplasty for ARS remain to be evaluated.

Conclusions

In conclusion, all the patients returned to normal life after keratoplasty. With a mean follow-up period of 3 years, grafts survived in 72.7% of ARS patients after keratoplasty, and 72.7% of eyes required additional glaucoma treatment. Eyes that underwent glaucoma surgeries before keratoplasty were more likely to exhibit markedly high IOP and require additional glaucoma therapy. Both PK and DSAEK resulted in similar outcomes with regard to IOP control, BCVA and ECL. Under sufficient synechiolysis and postoperative glaucoma management, patients with ARS can achieve transparent corneas, visual acuity improvement and pain remission after keratoplasty. Considering the better structural integrity and superiority of repeat keratoplasty with DSAEK, it may be the preferred procedure for irreversible keratoplasty secondary to ARS.

Author contributions JH conceived and supervised the study. All keratoplasty operations were performed by JH. TY and RP collected the data. TY and GX analyzed the data. TY wrote the manuscript. JH was considered corresponding author. TY was considered first author. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Consent for publication Written informed consent was obtained from each participant or their guardian before the data collection.

Ethical approval This study was approved by the Human Research Ethics Committee of Peking University Third Hospital (Approval Number: IRB00006761–M2018244) and was conducted in accordance with the Declaration of Helsinki.
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