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Corneal Transplantation under Difficult Conditions – Clinical Pictures, Indications, Technique, and Results.

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1.1 Summary

As the rate of partial thickness corneal transplantations has increased in the last decade, the need for penetrating keratoplasty (PKP) has decreased. Microsurgeons tend to avoid large-diameter PKP (LDPKP) because of the risk for intra- and postoperative complications. Nevertheless, PKP is still the treatment of choice in cases requiring transplantation of all corneal layers, such as combined endothelial and stromal disease, severe corneal opacity precluding evaluation of endothelium status, severe keratoconus, and complicated infectious keratitis.

In the first study, we report on the indications and outcomes of 8.5/8.6-mm excimer laser-assisted PKP. It could be shown that this type of PKP is an excellent treatment option in cases of ectatic disorders for which an 8.0-mm graft seems too small, and for corneal scars that require larger grafts to completely remove the lesion. This applies especially in cases of repeat PKP, in order to excise the previous graft completely. However, in complex cases of keratitis, the prognosis with 8.5/8.6-mm excimer laser-assisted PKP may be poor due to the consequences of the infectious disease itself.

In the second study, we assess the prevalence, clinical manifestations, required keratoplasties, follow-up, and outcomes in patients with Herpes Simplex Virus Keratitis. PKP was indicated in cases of scars impairing visual acuity, corneal decompensation, deep corneal ulcers, or corneal perforations. In this study, a total of 288 keratoplasties was performed. At the last follow-up, 90% of the elective PKPs, but only 55% of the emergency PKPs remained clear. The risk for emergency keratoplasty is expected to decrease further, due to good results with amniotic membrane transplantation (AMT) for the treatment of herpetic corneal ulcers.

In the third study, we report on the indications and outcomes of penetrating keratoplasties with a graft diameter >8.5 mm in severe corneal diseases. We concluded that complex cases of infectious keratitis unresponsive to conservative management and with a history of previous transplants require these oversized grafts up to 15 mm to remove the complete pathology and preserve the integrity of the eye. The visual outcomes are poor not only because of the well-known immunological risks of large-diameter keratoplasties but also because of the consequences of the infectious disease itself. Finally, 17% of these eyes required enucleation. This knowledge is important for adequate counseling of these patients preoperatively.

Difficult corneal predispositions may require special types of corneal transplantation “beyond routine”.

1.2 Zusammenfassung

Der Bedarf an perforierenden Keratoplastiken (PKP) ist zurückgegangen, da die Rate der lamellären Hornhauttransplantationen im letzten Jahrzehnt zugenommen hat. Mikrochirurgen neigen dazu, die PKP mit großem Durchmesser zu vermeiden, weil ein höheres Risiko für intra- und postoperative Komplikationen besteht. Dennoch ist die PKP immer noch die Behandlung der Wahl in Fällen, in denen alle Hornhautschichten transplantiert werden müssen, wie z. B. bei kombinierter Endothel- und Stromaerkrankung, schwerer Hornhauttrübung, die eine Beurteilung des Endothelstatus ausschließt, schwerem Keratokonus und komplizierter infektiöser Keratitis.

In der ersten Studie berichten wir über die Indikationen und Ergebnisse der 8,5/8,6-mm Excimerlaser-assistierten PKP. Es konnte gezeigt werden, dass diese Art der PKP eine hervorragende Behandlungsoption bei ektatischen Erkrankungen ist, für die ein 8,0-mm-Transplantat zu klein erscheint, sowie bei Hornhautnarben, die größere Transplantate erfordern, um die Läsion vollständig zu entfernen. Dies ist besonders bei Fällen von wiederholter PKP der Fall, um das vorherige Transplantat vollständig zu entfernen. In komplexen Fällen von Keratitis kann die Prognose bei 8,5/8,6-mm-Excimerlaser-assistierter PKP jedoch schlecht sein aufgrund von Folgen der Infektionskrankheit selbst.

In der zweiten Studie untersuchen wir die Prävalenz, die klinischen Manifestationen, die erforderlichen Keratoplastiken, das Follow-up und die Ergebnisse bei Patienten mit Herpes Simplex Virus Keratitis. Die PKP wurde bei visusbeeinträchtigenden Narben, Hornhautdekompensation, tiefen Hornhautulzera oder Hornhautperforationen indiziert. In dieser Studie wurden insgesamt 288 Keratoplastiken durchgeführt. Bei der letzten Nachuntersuchung waren 90% der elektiven PKPs, aber nur 55% der Notfall-PKPs klar. Es wird erwartet, dass das Risiko für Notfall-Keratoplastiken aufgrund der guten Ergebnisse bei der Amnionmembrantransplantation (AMT) zur Behandlung von herpetischen Hornhautulzera weiter abnimmt.

In der dritten Studie berichten wir über die Indikationen und Ergebnisse von perforierenden Keratoplastiken mit einem Transplantatdurchmesser >8,5 mm bei schweren Hornhauterkrankungen. Wir kamen zu dem Schluss, dass komplexe Fälle von infektiöser Keratitis, die nicht auf eine konservative Behandlung ansprechen und in der Vergangenheit bereits transplantiert wurden, diese übergroßen Transplantate bis zu 15 mm benötigen, um die gesamte Pathologie zu entfernen und die Integrität des Auges zu erhalten. Die visuellen Ergebnisse sind nicht nur wegen den bekannten immunologischen Risiken von Keratoplastiken mit großem Durchmesser, sondern auch wegen der Folgen der Infektionskrankheit selbst schlecht. Schließlich war bei 17% dieser Augen eine Enukleation erforderlich. Dieses Wissen ist wichtig für eine adäquate präoperative Beratung und Aufklärung der Patienten.

Schwierige korneale Ausgangssituationen erfordern nicht selten spezielle Typen von Hornhauttransplantationen „jenseits der Routine“.

2. Introduction

The rising number of partial-thickness corneal transplantations performed in the last decade has been associated with a reduced need for penetrating keratoplasty (PKP). In 2016, partial-thickness corneal grafts comprised over half of all keratoplasty procedures in the United States [11], and lamellar keratoplasties represented 60% of all keratoplasties in Germany [15]. However, PKP remains the treatment of choice in cases requiring transplantation of all corneal layers, for example, in combined endothelial and stromal disease, severe corneal opacity precluding evaluation of endothelium status, severe keratectasias, and complicated infectious keratitis [20].

For a successful PKP, the optimal graft size is as large as possible (for optical reasons) and as small as necessary (for immunological reasons) [44]. Microsurgeons tend to avoid large-diameter PKP due to the risk of intra- and postoperative complications. Mader and Stulting [35] reported that the graft's proximity to the limbal vasculature is a main reason for graft failure. Cherry et al. [9] found a positive correlation between graft size and allograft rejection. Kirkness et al. [30] reported a 46% 4-year survival probability in 17 grafts with a diameter ≥10 mm. These authors found that large-diameter PKP is associated with an overall markedly worse prognosis than smaller keratoplasties.

Theoretically, large-diameter PKP has the advantage of reduced astigmatism after surgery. In patients with keratoconus or pellucid marginal degeneration who underwent large diameter grafts (8.7−10.0 mm), Speaker et al [55] reported an average astigmatism of only 0.75 D after complete suture removal. Excimer laser-assisted keratoplasty has several advantages over other trephination techniques (e.g. mechanical and femtosecond laser-assisted), including a reduced amount of astigmatism, higher regularity of astigmatism, and better visual acuity following suture removal [44]. This is due to the avoidance of distortion and compression during trephination, yielding reductions of decentration, vertical tilt, and horizontal torsion of the graft in the recipient bed [46,50,62].

Large-diameter PKPs are indicated to treat conditions involving pathology that extends into the far peripheral cornea, such as pellucid marginal degeneration, keratoglobus, uncontrolled large corneal ulcers, fungal keratitis, and other severe melting corneal conditions that threaten vision or the eye itself [13,54]. In addition to rejection and glaucoma, another frequent complication of large-diameter PKP is recurrence of the previous disease. In these cases, a repeat even larger PKP may be needed. In order to be prepared for a recurrence, diagnostic PCR, culture, and histology from the excised tissue are mandatory [13].

The purpose of our work was to report the indications and outcomes of corneal transplantations under difficult conditions. In order to achieve this objective, we reviewed the files from patients between 2010-2016 who underwent 8.5/8.6mm excimer laser assisted penetrating keratoplasty in the Department of Ophthalmology at Saarland University Medical

Center. Knowing the results from this group of patients, we extended our objectives and we decided to analyze the data from patients who underwent PKP because of Herpes Simplex Virus associated complications as well as from patients who underwent a large-diameter PKP (>8.5mm) independently of the aforementioned reason.

3. Publications

3.1 Publication 1

8.5/8.6-mm Excimer Laser–Assisted Penetrating Keratoplasties in a Tertiary Corneal Subspecialty Referral Center: Indications and Outcomes in 107 Eyes

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Purpose: To report the indications and outcomes of 8.5/8.6-mm excimer laser assisted penetrating keratoplasties (PKPs) at a tertiary corneal subspecialty referral center.

Methods: This retrospective, descriptive, observational study included 107 PKPs performed in 96 patients (mean age, 53 ± 12 years). The patients' indications for surgery, best-corrected visual acuity, surface regularity index, surface asymmetry index, topographic astigmatism, central endothelial cell density, central corneal thickness, and graft status were recorded preoperatively, 6 weeks postoperatively, and before (12 ± 2 months) and after (19 ± 4 months) the suture removal.

Results: The surgeries included 48 primary PKPs and 59 repeat PKPs. The main indications were corneal ectatic disorders (50%), severe corneal keratitis (21%), and corneal scars (16%) in the primary PKP group and highly irregular astigmatism after PKP (51%) and previous graft decompensation (37%) in the repeat PKP group. From preoperative measurements to the last follow-up visit without sutures, we found significant improvements ($P < 0.001$ for all) in visual acuity (0.7 ± 0.3 LogMAR to 0.3 ± 0.2 LogMAR), surface regularity index (1.5 1.0), and surface asymmetry index (2.59 1.1). At the last follow-up, the mean outcome measurements did not significantly differ between the primary and repeat PKP groups. Overall, 89 grafts (83%) remained clear at the last follow-up.

Conclusions: In cases of ectatic disorders and highly irregular astigmatism after keratoplasty, 8.5/8.6-mm excimer laser assisted PKP seems to be an excellent treatment option, achieving a significant improvement in visual acuity.

Key Words: 8.5/8.6-mm excimer laser assisted keratoplasty, large-size keratoplasty, ectatic corneal diseases, keratoplasty for highly irregular astigmatism, repeat keratoplasty

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The increasing number of partial-thickness corneal transplants performed in the past decade has been associated with a reduced need for penetrating keratoplasty (PKP). In 2016, partial-thickness corneal grafts comprised over half of all keratoplasty procedures in the United States,[1] and lamellar keratoplasties represented 60% of all keratoplasties in Germany.[2] However, PKP remains the treatment of choice in cases requiring transplantation of all corneal layers, for example, in combined endothelial and stromal disease, severe corneal opacity precluding the evaluation of endothelial status, severe keratectasias, and complicated infectious keratitis.[3]

For a successful PKP, the optimal graft size is as large as possible (for optical reasons) and as small as necessary (for immunological reasons).[4] Microsurgeons tend to avoid large-diameter PKP because of the risk of intraoperative and postoperative complications. Mader and Stulting[5] reported that the graft's proximity to the limbal vasculature is a main reason for graft failure. Theoretically, large-diameter PKP has the advantage of reduced astigmatism after the surgery. In patients with keratoconus or pellucid marginal degeneration who underwent large-diameter grafts (8.7–10.0 mm), Speaker et al[6] reported an average astigmatism of 0.75 D after the complete suture removal.

Excimer laser–assisted keratoplasty has several advantages over other trephination techniques (eg, mechanical and femtosecond laser assisted), including a reduced amount of astigmatism, higher regularity of astigmatism, and better visual acuity after suture removal. This is because of the avoidance of distortion and compression during trephination, yielding reductions of decentration, vertical tilt, and horizontal torsion of the graft in the recipient bed.[4,7–9] In the present study, we aimed to report the indications and outcomes of 8.5-mm excimer laser–assisted PKPs in patients attending a tertiary corneal subspecialty referral center in Germany.

PATIENTS AND METHODS

For this retrospective observational study, we reviewed the files from all patients who underwent 8.5/8.6-mm-

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diameter excimer laser–assisted PKP at the Department of Ophthalmology of the Saarland University Medical Center between December 2010 and December 2016. A total of 107 surgeries were performed during this period.

Data were collected using the Microsoft Office Access database and analyzed with IBM SPSS Statistics for Windows, version 19.0 (IBM Corp, Armonk, NY). From all patients, we collected presurgical information regarding the indications for keratoplasty, uncorrected visual acuity, best-corrected visual acuity (BCVA), and topographic astigmatism. The analyzed postsurgical follow-up examinations occurred at 6 ± 1 weeks, 12 ± 2 months (with all sutures in), and 19 ± 4 months (after the removal of all sutures) after PKP. At the follow-up examinations, we recorded the uncorrected visual acuity, BCVA, topographic astigmatism, central corneal thickness, central endothelial cell count, surface regularity index (SRI), surface asymmetry index (SAI) from the TMS-5 topographer (Tomey GmbH, Erlangen, Germany), and graft status. One experienced surgeon (B.S.) performed 88 of the 107 surgeries (83%). The remaining 19 surgeries were performed by one of 6 experienced surgeons. All patients signed an informed consent before surgery.

Trephination was performed using the 193-nm excimer laser along metal masks with 8 orientation teeth/notches. Donor trephination from the epithelial side was performed using either the 193-nm excimer laser MEL 70 or the Schwind Amaris 750S and positioning a circular metal aperture mask on a corneoscleral button (16 mm diameter) fixed in an artificial anterior chamber under microscopic control (Fig. 1). After perforation, the remaining deep stromal lamellae <50 μm and Descemet membrane were cut with curved corneal microscissors. In all cases, the donor oversize was 0.1 mm. Host trephination was also performed with the excimer laser to perforation. A corresponding circular metal mask was used for recipient trephination (12.5 mm diameter). The mask does not require additional stabilization because of the horizontal orientation of the patient's head. Typically, 0 to 50 μm of the posterior stroma has to be completely cut with scissors in donor and recipient after the laser action stops.[9-11]

For each patient, surgery began with a peripheral iridotomy at the 12-o'clock position, and then, the donor button was temporarily fixed in the recipient bed with 8 interrupted sutures. In 92 surgeries, permanent wound closure was achieved using a 16-bite double running diagonal cross-stitch suture (10-0 nylon), according to Hoffmann.[12] In 15 cases, 24 interrupted sutures were used. The intended suture depth was at least 90% of the corneal thickness. In cases of wound gaping or graft override, additional interrupted sutures were used to ensure proper donor–host alignment at the end of surgery after the removal of the 8 cardinal sutures.[9,10]

Standard postoperative treatment included antibiotic eye drops, 5 times a day for 5 days, and steroid drops, 5 times a day, with a one-drop reduction every 6 weeks. Systemic oral steroids were indicated at a dose of 150 mg the first day, with a 20-mg reduction every 2 days. In cases of herpetic keratitis, oral acyclovir was prescribed at a dose of 400 mg, 5 times a day for 6 weeks, and then 400 mg, 2 times a day for at least 1 year.

Follow-up visits were scheduled at 6 weeks, 6 months, 12 months (after the removal of the first running suture or first half of interrupted sutures), and 18 months (after the removal of the second running suture or second half of interrupted sutures) after the surgery. Patients also had frequent control

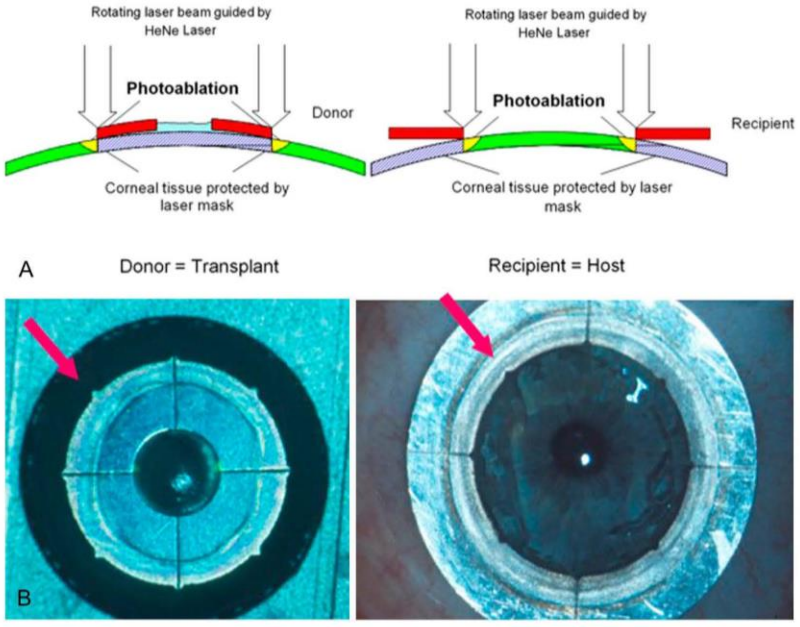

FIGURE 1. A, Schematic drawing of the principle of excimer laser trephination using metal masks: left, donor trephination; right, host trephination. B, Left: metal donor mask with 8 orientation teeth on a corneoscleral button fixed in an artificial anterior chamber; right: metal recipient mask with 8 orientation notches on the patient's cornea. The red arrows show the orientation teeth.

visits to their ophthalmologists: weekly during the first 6 weeks, monthly to 3 monthly thereafter, or immediately in emergency cases.

In this study, we only included patients who received excimer laser–assisted trephination. Since 1999, we have been using the excimer laser for more than 4500 PKP procedures. Only in case of strongly vascularized corneas are we using manual trephination because the excimer laser actions would stop as soon as the laser groove fills with blood. It was already published that the post-PKP astigmatism in laser-assisted keratoplasty is significantly lower compared with manual trephination.[9–11]

Statistical analyses were performed using software package SPSS/PC version 19.0 (IBM Corp). Comparisons between variables were performed using nonparametric tests: the Mann–Whitney *U* test for unpaired samples and the Wilcoxon test for paired samples. A *P* value <0.05 was considered statistically significant.

RESULTS

This study included a total of 107 PKPs performed in 96 patients. PKP was performed as primary PKP in 48 cases. In the other 59 cases, the patients had undergone a previous PKP. The mean patient age at the time of surgery was 53 ± 12 years, and 63 patients were men. A double running suture was used in 92 cases, and interrupted sutures were used in 15 cases.

Among the 96 patients, 7 required an 8.5-mm-diameter PKP in both eyes (6 had pellucid marginal degeneration, and one had endothelial decompensation because of congenital glaucoma). In 2 patients, the same eye was operated twice (one had Acanthamoeba keratitis, and the other had corneal decompensation after immune rejection). Only one patient required 3 PKPs for the same eye because of corneal decompensation after PKP (the primary diagnosis was congenital glaucoma). To facilitate the analysis of the data, the patients were divided into 2 groups: primary PKP group and repeat PKP group.

In the primary PKP group (n = 48), 40 PKPs (83%) were performed by the same experienced surgeon (B.S.). The main indications for primary 8.5/8.6-mm excimer laser–assisted PKP were ectatic corneal diseases (keratoconus, pellucid marginal degeneration, and keratoglobus) (Fig. 2), which constituted 50% of all indications in this group. Other indications for primary PKP included ulcers with different etiologies (21%) and corneal scars (17%).

In the repeat PKP group (n = 59), 48 PKPs (81%) were performed by the same experienced surgeon (B.S.). The main indications for repeat PKP with an 8.5 mm diameter were highly irregular astigmatism after PKP (51%) and endothelial decompensation (37%).

Tables 1 and 2 summarize the indications for PKP in both groups. Tables 3 and 4 summarize the patients' uncorrected visual acuity, BCVA, topographic astigmatism, SRI, SAI, central corneal thickness, and central endothelial cell density at different time points.

We observed a statistically significant ($P < 0.001$) increase in mean BCVA from 0.7 ± 0.3 LogMAR preoperatively to 0.3 ± 0.2 LogMAR at the last follow-up (with all sutures out). BCVA at the last follow-up visit did not significantly differ between the primary and repeat PKP groups ($P = 0.65$). The SRI and SAI values also showed a significant ($P < 0.001$) improvement at the last follow-up visit (SRI = 1.0, SAI = 1.1) compared with those at the preoperative measurements (SRI = 1.5, SAI = 2.59). These values at the last follow-up did not significantly differ between the primary and repeat PKP groups ($P = 0.07$).

The mean central corneal thickness was 542 ± 30 μm at 6 weeks after PKP and 559 ± 65 μm at the last follow-up without sutures. The mean central corneal thickness at the last follow-up did not significantly differ between the primary and repeat PKP groups ($P = 0.53$). The mean endothelial cell density was 2018 ± 430 cells/mm^2 at 6 weeks after PKP and 1764 ± 412 cells/mm^2 at the last follow-up, and the mean duration of the last follow-up was 19 ± 4 months (range 15–30 months) without sutures. The endothelial cell density at the last follow-up did not significantly differ between the primary and repeat PKP groups ($P = 0.40$).

The repeat PKP group included 30 eyes that exhibited a highly irregular astigmatism after PKP. In this subgroup, the mean BCVA significantly ($P < 0.001$) increased from 0.88 ± 0.3 LogMAR preoperatively to 0.34 ± 0.2 LogMAR at the last follow-up without sutures. The topographic astigmatism value decreased from −7.5 ± 3.5 D preoperatively to −5.5 ± 3.0 diopters at the last follow-up, although this change did not reach statistical significance ($P = 0.06$). The SAI significantly ($P < 0.001$) decreased from 2.2 ± 1.4 preoperatively to

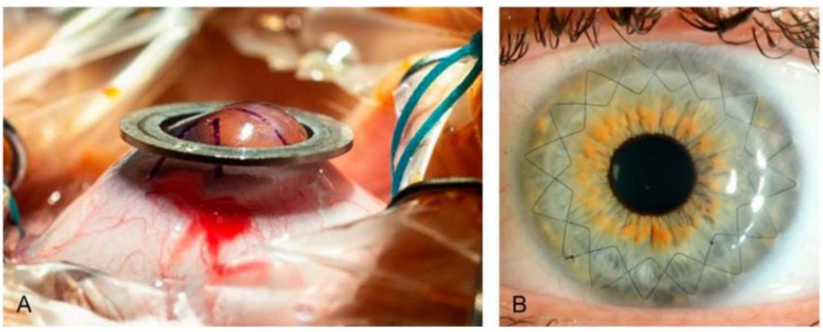

FIGURE 2. A, Side view of 8.5-mm metal recipient mask on a patient's cornea with severe pellucid marginal degeneration. B, Twenty-five-year-old male patient with pellucid marginal degeneration 6 months after excimer laser–assisted keratoplasty with double running cross-stitch sutures.

TABLE 3. Main Outcome Measurements at Multiple Time Points in the Primary PKP Group (n = 48)

	Uncorrected Visual Acuity LogMAR	BCVA LogMAR	Mean Astigmatism	Mean SRI	Mean SAI	Mean Central Corneal Thickness	Mean Endothelial Cell Density
Preoperative	1.2 ± 0.5	0.7 ± 0.3	−3.6 ± 3.1	1.6 ± 0.5	2.9 ± 1.3	525 ± 155	1945 ± 628
6 wk	0.8 ± 0.5	0.4 ± 0.2	−3.0 ± 2.7	1.2 ± 0.6	1.9 ± 1.3	541 ± 36	1988 ± 490
All sutures in	0.6 ± 0.4	0.2 ± 0.3	−3.5 ± 1.7	0.9 ± 0.8	1.3 ± 0.9	522 ± 47	1985 ± 462
All sutures out	0.7 ± 0.6	0.3 ± 0.3	−4.1 ± 3.0	1.0 ± 0.6	1.3 ± 1.2	548 ± 43	1688 ± 388
P	0.96	0.27	0.12	0.54	0.24	0.43	0.40

Data are presented as mean ± SD.
All sutures in, 12 ± 2 months after surgery; all sutures out, 19 ± 4 months after surgery.
P values are from the comparison between all sutures in and all sutures out.

ultima ratio within our armamentarium in case none of the listed approaches were applicable or successful. In addition, neither of the less invasive procedures can correct an irregular astigmatism. In their article in 2005 from another institution, Szentmáry et al[19] also reported an increase of astigmatism after the removal of the second running suture after repeat PKP. Why does this happen? To correct high irregular astigmatism after PKP by repeat PKP, we intend to excise the entire old graft. However, because we want to preserve at least 1.0 mm vertical and 1.5 mm horizontal distances of the new graft from the vascularized limbus, this is not always possible. This is especially true in case of small host corneas and/or decentered primary grafts that often come along with high/irregular astigmatism requiring surgical correction. In these cases, typically a crescent-shaped remnant of the old graft stays in place in one quadrant of the cornea resulting in a focal weakening like a hinge. This in turn may lead to a flattening in this very axis after the final suture removal because of the anterior movement of the graft in this axis. Indeed, our data show that the mean astigmatism was only 2.8 D with all sutures in place but increased to 5.0 D after the suture removal. Nevertheless, and this has also been shown in our Ophthalmology article from 1999, the surface regularity/symmetry after excimer laser trephination is significantly better than that after conventional trephination.[9,20] This leads to the fact that with excimer laser trephination after the suture removal, 2.8 D of the 3.0 D keratometric astigmatism can be tolerated subjectively in glasses on average. By contrast, with conventional trephination, only 4.2 D of the 6.1 D keratometric astigmatism is tolerated subjectively in glasses.[9] In the present study, even after suture removal, the SRI and SAI from the TMS-5 topographer improved significantly compared with preoperatively. We conclude that the most crucial determinant for spectacle correction is not the absolute amount of astigmatism but the regularity of astigmatism in a given range.

Several different studies show that the rate of chronic endothelial cell loss after PKP depends on the initial diagnosis.[21–23] However, in our study, the central endothelial cell density at the last follow-up did not significantly differ according to the diagnosis ($P = 0.40$). This may be explained by the high number of endothelial cells transplanted in an 8.6-mm graft. Moreover, at the last follow-up, the primary and repeat PKP groups did not significantly differ regarding BCVA, SRI, SAI, topographic astigmatism, or central corneal thickness values. Nowadays, large PKP is indicated not only for perforations or complicated infections but also in cases of ectatic conditions extending to the periphery, scars with stromal thinning, and repeat PKP to completely excise the old graft and recenter trephination (particularly in cases with high and/or irregular astigmatism).

In conclusion, our present results indicate that the 8.5/8.6-mm excimer laser–assisted PKP is an excellent treatment

TABLE 4. Main Outcome Measurements at Multiple Time Points in the Repeat PKP Group (n = 59)

	Uncorrected Visual Acuity LogMAR	BCVA LogMAR	Mean Astigmatism	Mean SRI	Mean SAI	Mean Central Corneal Thickness	Mean Endothelial Cell Density
Preoperative	1.2 ± 0.4	0.7 ± 0.3	−6.1 ± 4.2	1.5 ± 0.4	2.1 ± 1.5	628 ± 109	1764 ± 438
6 wk	0.6 ± 0.4	0.4 ± 0.2	−3.9 ± 2.5	0.9 ± 0.3	1.7 ± 1.5	543 ± 21	2056 ± 361
All sutures in	0.8 ± 0.6	0.3 ± 0.2	−2.8 ± 0.9	0.4 ± 0.2	0.8 ± 0.4	546 ± 37	1698 ± 460
All sutures out	0.5 ± 0.3	0.3 ± 0.2	−5.0 ± 3.3	0.9 ± 0.6	1.0 ± 0.7	574 ± 76	1677 ± 398
P	0.44	0.77	0.03	0.37	0.06	0.72	0.25

Data are presented as mean ± SD.
All sutures in, 12 ± 2 months after surgery; all sutures out, 19 ± 4 months after surgery.
P values are from the comparison between all sutures in and all sutures out.

option in cases of ectatic disorders for which an 8.0-mm graft seems too small and for corneal scars that require larger grafts to completely remove the lesion. Of the 34 such patients in our study, all exhibited a clear graft until the last follow-up. In addition, 8.5/8.6-mm excimer laser–assisted PKP represents a good treatment option in cases of highly irregular astigmatism, with such cases showing a significant improvement in BCVA because of increased corneal regularity. All 30 of these patients also showed clear grafts until the last follow-up. However, in complex cases of Acanthamoeba or even fungal keratitis, the prognosis with 8.5/8.6-mm excimer laser–assisted PKP may be poor because of the consequences of the infectious disease itself, and a larger graft may be needed from the beginning.

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3.2 Publication 2

Klinische Studie

Thieme

Herpes Simplex Virus Keratitis in a University Tertiary Referral Centre – Clinical Features and Surgical Approaches

Ausprägung und Therapie der Herpeskeratitis an der Universitäts-Augenklinik des Saarlandes

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ABSTRACT

Purpose To assess prevalence, clinical manifestations, required keratoplasties, follow-up, and outcome in patients with Herpes Simplex Virus Keratitis (HSK) attending a University Tertiary Referral Center.

Design Retrospective (12 years), descriptive, observational study.

Methods A total of 817 eyes with clinical diagnosis of HSK from 779 patients were classified by the type of presentation. We gathered data on the visual acuity, refraction, IOP, and required surgical procedures.

Results Stromal involvement including scars represented the most common diagnosis in our department and the main indication of penetrating keratoplasty (PKP). Epithelial keratitis (16%) presented with the best visual acuity at the first visit. Necrotizing keratitis represented 17% of the patients, 78% of whom required PKP; this group also had the worst visual acuity at first examination and was the main indication for emergency PKP. Among all eyes, 288 (35%) required PKP. A total of 230 (28%) PKPs were elective procedures and 58 (7%) PKPs were performed as emergency procedures. Two patients with quiet endothelial decompensations after recurrent HSV endotheliitis were treated with DMEK and had good visual outcomes without HSV recurrence at last follow-up.

Conclusions HSK is a prevalent disease with severe consequences when not treated appropriately and on time. Even when making an accurate diagnosis, the disease can be extremely aggressive, with all the implications it brings to the patients and health system. Elective PKP had better outcomes in terms of visual acuity and clear graft percentage compared to emergency PKP.

ZUSAMMENFASSUNG

Hintergrund Beurteilung der Prävalenz, der klinischen Manifestationen, der erforderlichen Keratoplastiken, der Nachsorge und der Ergebnisse bei Patienten mit Herpes-simplex-Virus-Keratitis (HSK), die ein tertiäres universitäres Referenzzentrum besuchen.

Design Retrospektive (12 Jahre), deskriptive Beobachtungsstudie.

Methoden Insgesamt wurden 817 Augen mit der klinischen Diagnose HSK von 779 Patienten nach der Art der Präsentation klassifiziert. Wir sammelten Daten zur Sehschärfe, Refraktion, IOD und den erforderlichen chirurgischen Eingriffen.

Ergebnisse Die stromale Beteiligung einschließlich Narben stellte die häufigste Diagnose in unserer Abteilung und die

Thieme

Hauptindikation für eine perforierende Keratoplastik (PKP) dar. Patienten mit epithelialer Keratitis (16%) stellten sich beim ersten Besuch mit der besten Sehschärfe vor. Die nekrotisierende Keratitis machte 17% der Patienten aus, von denen 78% eine PKP benötigten; diese Gruppe hatte auch die schlechteste Sehschärfe bei der Erstuntersuchung und war die Hauptindikation für eine PKP à chaud. Von allen Augen benötigten 288 (35%) eine PKP. Insgesamt 230 (28%) PKPs waren elektive Eingriffe und 58 (7%) PKPs wurden à chaud durchgeführt. Zwei Patienten mit ruhigen endothelialen Dekompensationen nach rezidivierender HSV-Endotheliitis wurden mit DMEK behandelt und hatten bei der letzten Nachbeobachtung einen guten Visus ohne HSV-Rezidiv.

Schlussfolgerungen HSK ist eine weitverbreitete Erkrankung mit schwerwiegenden Folgen, wenn sie nicht angemessen und rechtzeitig behandelt wird. Selbst wenn die richtige Diagnose gestellt wird, kann die Krankheit extrem aggressiv sein, mit all ihren Auswirkungen auf die Patienten und das Gesundheitssystem. Die elektive PKP hatte im Vergleich zur PKP à chaud bessere Ergebnisse in Bezug auf die Sehschärfe und das Transplantatüberleben.

Introduction

Infections by herpes simplex virus (HSV) represent the primary cause of unilateral corneal blindness due to infectious causes in developed countries. With the exception of neonatal cases, which are largely caused by HSV 2, more than 95% of ocular infections are caused by HSV 1. Ocular infection is mainly caused by reactivation of the latent virus in the Gasser ganglion of the trigeminal nerve [1–3].

The primary ocular infection is commonly an epithelial keratitis, whereas stromal keratitis or associated anterior uveitis is rare as the initial presentation. The event is typically self-limiting, but treatment with antivirals shortens the symptom duration [2].

Types of corneal manifestation include epithelial keratitis, stromal keratitis (necrotising and interstitial), endotheliitis, neurotrophic keratopathy, and stromal scars. Infectious epithelial keratitis is the most common presentation of keratitis. The typical epithelial lesion consists of dichotomic ramifications, linear lesions with terminal bulbs, and swollen epithelial borders that contain the live virus. These lesions can extend and become a geographic lesion. The possible sequelae of this presentation include stromal keratitis, neurotrophic keratopathy, and scars [4].

Stromal keratitis represents just 2% of initial presentations [5], but up to 61% of recurrences. The stroma may be affected by different mechanisms, and it is important to classify the condition accurately. The primary forms of stromal keratitis are subdivided into necrotising or interstitial [4–6]. The necrotising form is an aggressive variant caused by direct virus infection of the corneal stroma with a severe immunological reaction. The necrotising form can progress rapidly to corneal perforation if treatment is not applied timely and effectively [4, 5]. The interstitial or non-necrotising variant is thought to be caused by viral antigens retained in the stroma, which activate a series of antigen-antibody reactions with complement involvement causing inflammation. The clinical course tends to be chronic, requiring the long-term use of steroids to suppress the immune response. Non-desired consequences from this variant are scaring, stromal thinning, ectasia, neovascularisation, and lipid deposits, which may lead to significant vision loss [4, 5]. Endotheliitis or disciform keratitis manifests as keratic precipitates, iritis, and epithelial and stromal oedema. The primary localisation of endotheliitis is at the endothelial level. Although the condition is also an immune reaction, it should not be classified as stromal because signs of stromal inflammation, such as neovascularisation or infiltrates, are absent. The exact pathogenesis of endotheliitis in HSV is not clear. The clinical manifestations can be subdivided into "disciform" (by far the most common form), linear, or diffuse disease patterns [4, 5].

Neurotrophic keratopathy is a risk in patients who have previously suffered epithelial or stromal herpetic keratitis and is typically a late complication of the disease. This pathology is neither infectious nor immune-mediated but is due to corneal hypothesia or anesthesia due to inflammation and damage of the axonal trigeminal nerves caused by the virus with decreased lacrimal production. The epithelial erosions may form persistent epithelial defects and, later, neurotrophic ulceration. Further complications of this variant could be degradation and thinning of the stroma, stromal scars, neovascularisation, necrosis, perforations, and secondary bacterial infections [4, 5, 7].

Corneal scars typically represent the late stage of all forms of stromal HSV keratitis. They are typically disciform, may occur with or without vascularisation, and accompanying stromal thinning [8, 9].

The diagnosis of primary and recurrent ocular HSV infection primarily depends on a detailed ophthalmic examination in which corneal sensitivity testing is of great importance to distinguish from other infectious diseases. Diagnostic tools that can help with the definitive diagnosis are viral culture, immunological tests, and polymerase chain reaction (PCR) [10, 11].

Treatment of herpetic keratitis depends on the mechanism by which the virus affects the cornea. Therefore, an accurate diagnosis is crucial not only for the resolution time, but also for the prevention of undesired complications. Antivirals are given in cases of active virus replication and as viral prophylaxis; steroids are used in cases of immunological involvement. In selected cases (persistent epithelial defects, therapy-resistant ulcerations, visually disturbing scars, and perforations), a surgical approach is required, such as tarsorrhaphy, amniotic membrane transplantation (AMT), or keratoplasty, either lamellar or penetrating [11–13].

The purpose of this study was to assess the prevalence, clinical manifestations, required keratoplasties, follow-up, and outcome in patients with herpes simplex virus keratitis (HSK) presenting at the Department of Ophthalmology at Saarland University Medical Centre as a tertiary referral centre with corneal subspecialty.

Patients and Methods

For this study, we reviewed all of the files from patients clinically diagnosed with HSV ocular disease at the Department of Ophthalmology at Saarland University Medical Centre from January 2006 to April 2018. A total of 779 patients and 817 eyes were included. The information was collected and analysed in a Microsoft Office Access database. All patients were classified by the type of presentation of HSV eye disease. For all patients, we gathered data on visual acuity, medical treatment, refraction, intraocular pressure (IOP), and the presence of scars in the cornea, vascularisation, and surgical procedure (keratoplasties and AMT).

The topical antivirals delivered to the patients in our department included ganciclovir gel for most cases. Before the introduction of ganciclovir, we applied acyclovir ointment. Systemic antivirals included either acyclovir or valacyclovir.

The topical steroids prescribed to the patients were prednisolone or dexamethasone, while loteprednol drops were used in steroid responders. Systemic methylprednisolone was added to the treatment plan in cases of non-necrotising "interstitial" keratitis and endotheliitis. When topical antibiotics were indicated, the patients received either ofloxacin or moxifloxacin. The cyclopegic drug was atropine.

In general, the treatment was as follows:

- Epithelial keratitis: antiviral gel 5 times a day and in cases with suspect bacterial superinfection, antibiotic drops 5 times per day for 2 or 3 weeks.
- Stromal necrotising keratitis: antiviral gel plus antibiotic drops 5 times per day, cyclopegic drops 2 times per day. After 2–3 days of antiviral and antibacterial coverage, the steroids were initiated carefully. Systemic acyclovir was given in doses of 5 × 400 mg/day or 5 × 800 mg/day (in very severe cases and VZV infection) for 4 weeks and then 2 × 400 mg/day for at least 6 months in all cases. In cases of non-responders to acyclovir, we typically used valacyclovir intravenously in a dosage of 3 × 500 mg. We never used famciclovir.
- Interstitial, endothelial, and keratouveitis: steroid drops and antiviral ganciclovir gel 5 times a day for at least 2 weeks, and tapered over 4 to 8 weeks. Systemic antivirals were prescribed 5 × 400 mg/day for 4 weeks and then 2 × 400 mg/day for at least 6 months in order to reduce the risk of recurrence. Antiglaucoma drops were also utilised in cases of IOP > 22 mmHg, and prostaglandin drops were avoided due to the risk of HSK recurrence.
- Neurotrophic: all the "unnecessary" drops (incl. antivirals, steroids, and all preservatives) were discontinued; the patients received preservative-free eye drops, and in cases of severe epithelial defects, autologous serum and therapeutic contact lenses. Cenegermin (Oxervate) was not used in the study population.

In cases of persistent epithelial defects or corneal ulceration, AMT was performed by one of nine different surgeons. Depending on the depth of the lesion, it was used as a patch (one layer) 16 mm in diameter, as a graft, or as a sandwich technique (combination of graft and patch). When it was used as a patch, it was fixed with a running 10–0 nylon suture; when it was used as a graft, interrupted sutures were preferred. All patients received a 17-mm diameter therapeutic contact lens [14 – 16]. The treatment included antibiotic drops 4 times a day, and antivirals (ganciclovir gel) 5 times per day. A low dosage of unpreserved steroid drops without phosphate (e.g., Dexapos COMOD 1.0 mg/mL eye drops 2–3×/day) was used after keratoplasty to prevent immune reactions. After a 4-week follow-up interval, with regular control visits with their ophthalmologists, contact lens and sutures were removed.

Penetrating keratoplasty (PKP) was indicated in cases of scars impairing visual acuity, corneal decompensation, deep corneal ulcers, or corneal perforations. PKPs were performed by one of nine different surgeons. In most cases, the trephination was made with the aid of an excimer laser [17]. Interrupted sutures (24 stitches) were preferred in most cases, especially in cases with defects in Bowman's layer and in emergency PKPs, but a double running suture was performed in cases of central corneal scars without vascularisation. The standard treatment included antibiotic drops 5 times a day for 5 days, steroid drops 5 times a day with one drop reduction every 6 weeks, and oral acyclovir prescribed at a dose of 5 × 400 mg/day for 6 weeks and then 2 × 400 mg/day for 1 year. Systemic oral steroids were indicated at 100 mg the first day with 20 mg reductions every 2 days and then stopped. The follow-up visits were scheduled at 6 weeks, 6 months, and 1 year after the surgery, with frequent control visits (weekly during the first 6 weeks, later every month) with their ophthalmologists or immediately in emergency cases.

Despite these general treatment recommendations, treatment regimens were individualised for each patient.

All data were collected anonymously. The Ethics Committee of Saarland (Ärztekammer des Saarlandes, Körperschaft öffentlichen Rechts, Faktoreistrasse 4, 66111 Saarbrücken; ethikkommission@aeksaar.de; President: Prof. Dr. U. Grundmann) acknowledged the publication of this manuscript (Saarbrücken, 30.07.2020) without further obligations from our side.

Results

Demographics

We evaluated 817 affected eyes from 779 patients; 386 patients (49.5%) were male and 393 (50.5%) were female. The mean age of the study population was 62 ± 22 years (9–89 years). The mean spectacle-corrected visual acuity (SCVA) at first examination was 0.5 ± 0.2 SD log MAR. Regarding comorbidities, 9% of the patients had arterial hypertension, 5% diabetes mellitus, 3% thyroid disease, and 3% autoimmune disease.

The types of herpetic corneal disease are summarised in ▸ **Table 1**.

As many patients come to the clinic with a stromal scar and, in many cases, it was not possible to determine the exact type of keratitis, we included a group of stromal scars, knowing that they have had previously repeated stromal keratitis. We divided stromal involvement into three different groups: stromal scars, interstitial keratitis, and necrotising keratitis.

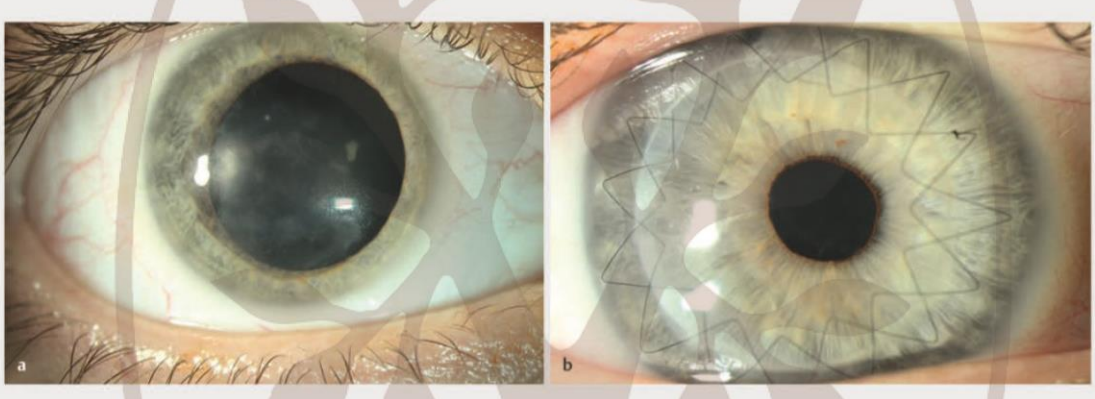
Stromal scars in inflammatory quiescence represented the most common diagnosis with 192 cases (24%) in our department; 66 of these patients had neovascularisation and 100 were treated

3.2 Publication 2

▸ **Table 1** Types of herpetic corneal disease. Mean astigmatism and mean best-corrected visual acuity (BCVA) measured with spectacles and mean IOP values obtained at first examination in our department.

Type of keratitis	Number of cases	Mean astigmatism (diopters)	Mean BCVA (log MAR)	Mean IOP	Number of AMTs	Number of PKPs
Epithelial	132 (16%)	− 2.0 ± 1.3	0.2 ± 0.2	14 ± 4.0	14	0
Necrotising	142 (17%)	− 4.1 ± 2.5	0.6 ± 0.2	13.0 ± 3.5	70	111
Interstitial	47 (6%)	− 2.3 ± 1.6	0.3 ± 0.3	14.2 ± 3.7	1	5
Endothelial	140 (17%)	− 2.5 ± 2.1	0.4 ± 0.2	15.0 ± 5.8	3	37
Keratouveitis	84 (10%)	− 1.8 ± 1.35	0.4 ± 0.2	16.5 ± 8.0	3	7
Neurotrophic	22 (3%)	− 5.75 ± 5.6	0.5 ± 0.3	12.0 ± 3.7	10	4
Scars	192 (24%)	− 4.0 ± 3.0	0.5 ± 0.2	13.6 ± 3.8	4	100
Overlap	58 (7%)	− 3.4 ± 2.2	0.5 ± 0.3	14.5 ± 3.5	24	24
Total	817 (100%)	− 3.20 ± 2.6	0.5 ± 0.2	14.2 ± 5.4	129	288

AMT, amniotic membrane transplantation; PKP, penetrating keratoplasty. Overlap disease: cases in which patients had two documented types of corneal involvement.



▸ **Fig. 1** Patient with a history of recurrent herpetic keratitis episodes. **a** Preoperatively, avascular stromal scars; BCVA 20/200. **b** Six months after excimer laser-assisted penetrating keratoplasty (8.0/8.1 mm) with double running cross-stitch sutures; BCVA 20/50.

with keratoplasty (▸ **Fig. 1**). Epithelial keratitis was the keratitis with the best BCVA at the first examination, and it also had the lowest astigmatism. In contrast, necrotising keratitis had the worst BCVA at the first examination visit and required the most surgical procedures.

We refer to "overlapping" disease in cases in which patients were documented with two types of corneal involvement, which represented 7% of the sample. The most common associations were epithelial plus endothelial.

Penetrating keratoplasty

A total of 245 patients (30%) from the cohort required PKP. In addition, 29 (10%) of the transplanted patients required a second keratoplasty surgery, 3 of which had additional subsequent operations. Five patients required bilateral keratoplasty, and a total of 288 keratoplasties were performed.

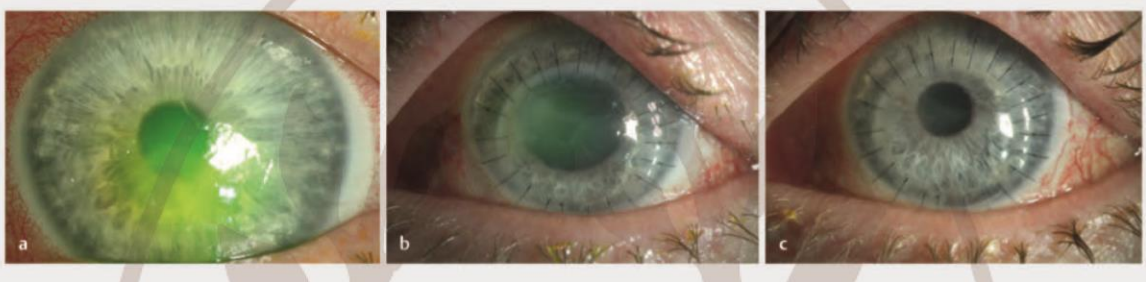
The initial mean BCVA was 1.0 ± 0.2 log MAR, and the mean BCVA at last examination was 0.7 ± 0.17 log MAR. The mean follow-up period was 17.5 ± 23 months. Seventy-two percent of all performed keratoplasties remained clear in the last follow-up visit.

Twenty-five patients have already had one or more PKPs in another hospital, and 21 (85%) of them required a new transplant. The reasons for a new transplant were corneal scar in the transplant (60%), transplant endothelial decompensation (28%), perforated ulcers (8%), and high astigmatism (4%).

Eighty percent of keratoplasties were elective and 20 percent were emergency keratoplasties. In a separate analysis of the elective keratoplasties and emergency keratoplasties, we obtained the results in ▸ **Table 2**.

▶ **Table 2** Penetrating keratoplasties performed. Results after PKP for HSV keratitis. Mean SCVA before surgery and at last follow-up, mean astigmatism (objective refraction) and clear graft values provided at last follow-up visit, mean IOP post-keratoplasty throughout the follow-up period. Clear graft as estimated by slit lamp.

	PKP (n)	Mean follow-up period (months)	Mean SCVA pre-PKP (log MAR)	Mean BCVA post-PKP (log MAR)	Mean astigmatism at last follow-up post-PKP (D)	Mean IOP post PKP (mmHg)	Clear graft at last visit
Elective	230	18 ± 22	0.9 ± 0.16	0.5 ± 0.2	−4.4 ± 2.5	14.0 ± 3.7	90%
Emergency	58	16 ± 25	1.2 ± 0.1	0.8 ± 0.19	−5.9 ± 2.3	13.0 ± 3.9	55%



▶ **Fig. 2** **a** Patient with necrotising herpetic keratitis BCVA 20/400. **b** Persistent epithelial defect in the transplant; BCVA 20/630. **c** Four weeks after AMT as a patch, the epithelial defect was healed; BCVA 20/200.

Amniotic membrane transplantation

A total of 129 AMTs were performed. Necrotising herpetic keratitis represented the most common diagnosis that required this procedure. The indications for this procedure were either treatment of a persistent epithelial defect as single-layer AMT (patch; 60%) or, in cases with deep stromal ulcers, AMT was performed using a sandwich technique (graft and patch; 40%, ▶ **Fig. 2**).

Descemet membrane endothelial keratoplasty

Only two patients underwent Descemet membrane endothelial keratoplasty (DMEK) in quiet endothelial decompensations after recurrent HSV endotheliitis with good results. In one of the patients, the cornea was clear and the BCVA (20/32) was 0.2 log MAR after 18 months of follow-up. In the second patient, DMEK was combined with phacoemulsification and IOL (intraocular lens) implantation (triple procedure), and after 24 months of follow-up, the graft was clear with a BCVA (20/20) of 0 log MAR (▶ **Fig. 3**).

Discussion

It has been more than 20 years since the Herpetic Eye Disease Study Group presented the first recommendations for the management of patients suffering from herpetic keratitis. The current general concepts of treatment include different topical antivirals with less corneal toxicity, such as acyclovir and ganciclovir, and new surgical procedures, such as amnion membrane transplantation and DMEK.

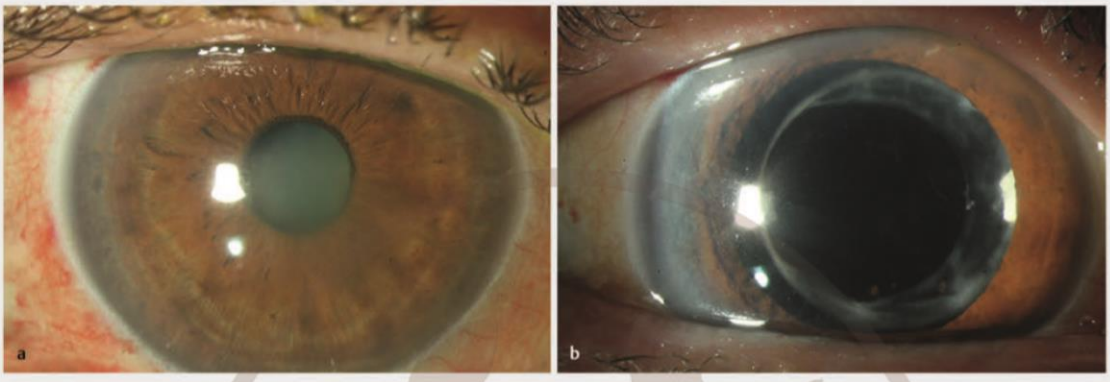
The diagnosis of herpetic eye disease can be challenging because it may have similar lesions as other pathogens; this ability to mimic other diseases has led some authors to describe it as a “chameleon disease” [8, 9, 11].

The patients in the present study seem to be quite old (62 years on average). This may be due to a selection bias in a tertiary university-based referral centre and may be explained, at least in part, by the finally relatively serious consequences of recurrent HSV keratitis over years, which was treated outside the university in the beginning, when the patients were younger.

Although overall epithelial recurrences appear to be the most prevalent type of HSV keratitis, the most common presentation in this university-based study was stromal involvement (47% of eyes). Despite the stromal necrotising type being reported as the least common form of keratitis, it was present in 17% of our study population. This may be explained by the fact that the study took place in a tertiary, highly specialised corneal subspecialty centre. The treatment was aggressive in this scenario, and steroids were only used following a few days of antiviral and antibacterial coverage. A total of 111 eyes (78%) from the stromal necrotising keratitis required keratoplasty.

The endothelial variant was the second most common variant in our study. In this group, two patients were treated with DMEK with excellent visual acuity results and without herpetic keratitis recurrence within 2 years of follow-up. In 2018, Asi et al. [18] reported a case of herpetic endotheliitis treated with DMEK that resulted in 20/20 visual acuity, without recurrence, suggesting that it can be a good surgical option for patients with endothelial decompensation. Among the patients with elevated IOP, the use of prostaglandins was avoided because of their proinflammatory effects and their potential risk to act as a trigger of disease recurrence [16, 19].

3.2 Publication 2



▶ **Fig. 3** **a** Patient with endothelial disciform herpetic keratitis and endothelial decompensation. **b** 24 months after DMEK (7.5 mm diameter) combined with phacoemulsification and IOL implantation; BCVA 20/20.

Different studies have reported that the incidence of bilateral disease ranges between 1 and 10% [5]. In this study, 38 patients were diagnosed with bilateral disease, representing 5% of the patients. Bilateral infections tend to be more aggressive, are more common in children, and should raise the question of immune dysfunction [20].

In this study, a total of 288 keratoplasties were performed. At last follow-up, 90% of the elective PKPs, but only 55% of the emergency PKPs, remained clear. The risk for emergency keratoplasty is expected to decrease further due to good results with AMT for the treatment of herpetic corneal ulcers [12–13].

Importantly, PCR technology may be extremely helpful in establishing the diagnosis of HSV infection [21–23], though in cases of interstitial keratitis, PCR can often remain negative. McGilligan et al. [24] hypothesised that, because interstitial keratitis is caused by an immune response instead of an active viral infection, PCR may be negative. Another study showed that there was an 80% decrease in the detectable virus by PCR in patients taking 800 mg acyclovir daily [25]. This finding underlines the importance of accurate clinical examination, as laboratory diagnoses can never be 100% exact. However, this finding also sheds light on the complexity of the pathogenesis of HSV keratitis.

This study has at least two limitations: the first one is that it was a retrospective study with some missing information, especially concerning patient history, and the second one is that it was performed in a referral centre for corneal disease that does not necessarily represent the typical distribution of the different types of herpetic keratitis. The bias of this study is towards more severe manifestations of HSV keratitis and towards more keratoplasty cases.

Nevertheless, we can conclude that despite improvements in diagnostic techniques and medical and surgical management, herpetic keratitis is a prevalent disease with severe consequences when not treated appropriately and in a timely manner. Even when making an accurate diagnosis, the disease can be extremely aggressive, with all the implications it brings to the patients and health system. Elective PKP has a better outcome in terms of visual acuity and clear graft percentage compared to emergency PKP. Therefore, amniotic membrane transplantation in the acute stage of the ulcerative keratitis can help postpone PKP until a quiet stage is reached, which will yield a better postoperative prognosis.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Klinische Studie

Thieme

Large-Diameter Penetrating Keratoplasties are Mostly Due to Very Severe Infectious Keratitis and Cannot Always Prevent Secondary Enucleation

Perforierende Keratoplastiken mit großem Durchmesser sind meist auf eine sehr schwere infektiöse Keratitis zurückzuführen und können eine sekundäre Enukleation nicht immer verhindern

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ABSTRACT

Purpose To report the indications and outcomes of penetrating keratoplasties with a graft diameter > 8.5 mm in severe corneal diseases at the Department of Ophthalmology at Saarland University Medical Centre.

Study Design Retrospective (6 years), descriptive, and observational.

Methods Thirty-five large-diameter penetrating keratoplasties (LDPKPs) in 27 patients (mean age, 62 ± 22 years) were performed from March 2010 to December 2016. The indication for surgery, number of previous corneal transplantations, best-corrected visual acuity (BCVA) before surgery, intraocular pressure, graft status, and BCVA at last follow-up were recorded.

Results Infectious keratitis represented 83% of the indications (of those, 45% fungal). The mean corneal graft diameter was 10.8 ± 1.7 (min 8.75, max 15.0) mm. Twenty-three eyes (65% absolute) had at least one previous penetrating keratoplasty (mean graft size, 9.2 ± 1.6 mm). The mean pre-surgery BCVA was 1.96 ± 0.23 logMAR. With a mean follow-up period of 20.2 ± 13.4 months, the mean BCVA was 1.57 ± 0.57 logMAR at last follow-up. Overall, 12 grafts (35%) remained clear until the last follow-up, and in 23 grafts (65%), the primary disease recurred, or corneal decompensation developed. Up to the last follow-up, 6 eyes (17%) had to be enucleated.

Conclusions In complex cases of infectious keratitis requiring a LDPKP to remove the complete pathology and preserve eye integrity, the visual outcomes are generally expected to be poor, not only because of the well-known risks of LDPKP but also because of the consequences of the infectious disease itself. This knowledge is important for adequate counselling of the patient preoperatively.

ZUSAMMENFASSUNG

Ziel Bericht über Indikationen und Ergebnisse von perforierenden Keratoplastiken mit Transplantatdurchmesser > 8,5 mm bei schweren Hornhauterkrankungen an der Klinik für Augenheilkunde des Universitätsklinikums des Saarlandes.

Design Retrospektive (6 Jahre) und deskriptive Beobachtungsstudie.

Methoden Von März 2010 bis Dezember 2016 wurden 35 „Large-Diameter perforierende Keratoplastiken" (LDPKPs) bei 27 Patienten (mittleres Alter 62 ± 22 Jahre) durchgeführt.

Erfasst wurden die Indikation zur Operation, die Anzahl der vorausgegangenen Hornhauttransplantationen, der bestkorrigierte Visus (BCVA) vor der Operation, der Augeninnendruck, der Transplantatstatus und der BCVA beim letzten Follow-up.

Ergebnisse Die infektiöse Keratitis machte 83% der Indikationen aus (davon 45% Pilzkeratitis). Der mittlere Durchmesser des Hornhauttransplantats betrug 10,8 ± 1,7 mm (mind. 8,75, max. 15,0 mm). 21 Augen (65% absolut) hatten mindestens eine vorangegangene perforierende Keratoplastik (mittlere Transplantatgröße 9,2 ± 1,6 mm). Der mittlere BCVA vor der Operation betrug 1,96 ± 0,23 logMAR. Bei einer mittleren Nachbeobachtungszeit von 20,2 ± 13,4 Monaten betrug der mittlere BCVA beim letzten Follow-up 1,57 ± 0,57 logMAR. Insgesamt blieben 12 Transplantate (35%) bis zur letzten Nachuntersuchung klar und bei 23 Transplantaten (65%) trat die primäre Erkrankung erneut auf oder es entwickelte sich eine Hornhautdekompensation. Bis zum Ende des Beobachtungszeitraums mussten 6 Augen (17%) enukleiert werden.

Schlussfolgerungen Bei komplexen Fällen von infektiöser Keratitis, die eine LDPKP erfordern, um die gesamte Pathologie zu entfernen und die Integrität des Auges zu erhalten, sind die zu erwartenden Visusergebnisse im Allgemeinen eher ungünstig, nicht nur wegen der bekannten Risiken der LDPKP, sondern auch wegen der Folgen der Infektionskrankheit selbst. Dieses Wissen ist wichtig für eine adäquate Beratung und Aufklärung der Patienten präoperativ.

Introduction

As the rate of partial thickness corneal transplantations has increased in the last decade, the need for penetrating keratoplasty (PKP) has decreased. In the United States in 2016, more than half of all keratoplasties were partial thickness corneal grafts [1]. In the same year in Germany, lamellar keratoplasties represented 60% of all keratoplasties [2]. Nevertheless, PKP is still the treatment of choice in cases requiring transplantation of all corneal layers, such as combined endothelial and stromal disease, severe corneal opacity precluding evaluation of endothelium status, severe keratoconus, and complicated infection keratitis [3].

Recently, we reported that an 8.5/8.6 mm excimer laser-assisted keratoplasty is a particularly good option for primary procedures in ectatic corneal diseases but especially for repeat PKP due to high/irregular astigmatism after PKP [4]

Microsurgeons tend to avoid large-diameter PKP (LDPKP) because of the risk for intra- and postoperative complications. The proximity of the graft to the limbal vasculature has been reported by Mader and Stulting as a main reason for graft failure [5]. Cherry et al. found a positive correlation between graft size and allograft rejection [6]. Kirkness et al. reported a 46% 4-year survival probability in 17 grafts with a diameter ≥ 10 mm [7]. These groups found that LDPKP is associated with an overall markedly worse prognosis than smaller keratoplasties.

One theoretical advantage of LDPKP is the reduced astigmatism after the surgery. Speaker et al. reported an average astigmatism of 0.75 D after complete suture removal in patients with keratoconus or pellucid marginal degeneration who underwent LDPKP (8.7 to 10.0 mm) [8].

LDPKPs are indicated to treat conditions involving pathology that extends into the far peripheral cornea, such as pellucid marginal degeneration, keratoglobus, uncontrolled large corneal ulcers, fungal keratitis, and other severe melting corneal conditions that threaten vision or the eye itself [9, 10].

In addition to rejection and glaucoma, another frequent complication of LDPKP is the recurrence of the previous disease. In these cases, a repeat LDPKP may be needed. In order to be prepared for a recurrence, diagnostic PCR, culture, and histology from the excised tissue are mandatory [9].

The purpose of this study was to report the indications and outcomes of penetrating keratoplasties with a graft diameter > 8.5 mm in severe corneal diseases in patients attending a tertiary referral center with corneal subspecialty.

Patients and Methods

For this retrospective, observational study, we reviewed all files from patients who had a PKP with a diameter > 8.5 mm at a tertiary referral center from March 2010 until December 2016. A total of 35 eyes of 27 patients were included.

The data were collected and analyzed in Microsoft Office Excel. At the examination before surgery, the clinical data recorded were age, sex, best-corrected visual acuity (BCVA), intraocular pressure (IOP), indication for the LDPKP, and number and size of previous keratoplasties. At the last follow-up examination, the data gathered included BCVA, IOP, state of the corneal graft, histopathology and microbiology reports, treatment, and any indication for further PKP or enucleation.

Six experienced corneal surgeons performed the PKPs. All patients signed informed consent before surgery. Trephination was performed in donors as well as in patients using a hand-held trephine; the incision was completed using curved corneal microscissors. Four cardinal 10–0 nylon sutures were positioned to secure the donor–recipient apposition, followed by at least 28 interrupted sutures. The intended depth of the sutures was at least 90% of the total corneal thickness. All suture knots were rotated and buried in the donor stroma. The trephine size for the recipient cornea was based on the diameter necessary to presumably remove the entire diseased part of the cornea. Our primary goal was to cure the underlying disease. To achieve this goal, the excision in the host cornea had to be placed, to some extent, eccentrically but with minor limbal involvement for larger graft sizes, especially in fungal and bacterial keratitis cases. However, we had to perform a sclerokeratoplasty with major limbal involvement in only two cases. The graft diameter ranged between 8.75 mm and 15.0 mm with a mean value of 10.8 ± 1.7 mm. The graft oversize depended on the graft size: for the 8.75 grafts, the oversize was 0.25 mm (in which a Hessburg-Barron Trephine was used); for the 9.5, 10.0, and 10.5 mm grafts, the oversize was 0.5 mm; and

▸ **Table 1** Preoperative date and postoperative outcomes

LDPKP indication	LDPKP No. (%)	Eyes with previous PKP (%)	Mean number of previous PKPs	Mean graft size (mm)	BCVA before PKP (logMAR)	BCVA at last follow-up (logMAR)	Follow-up time (months)	Clear graft at last follow-up (%)	Enucleation (%)
Fungal keratitis	13 (37% A)	8 (61% R)	1.0 ± 1.0	11.0 ± 1.3	1.96 ± 0.17	1.69 ± 0.46	11.3 ± 7.8	3 (23% R)	2 (15% R)
Bacterial keratitis	8 (23% A)	5 (62% R)	2.1 ± 2.4	10.6 ± 1.9	2.02 ± 0.70	1.53 ± 0.70	11.0 ± 15.3	3 (37% R)	3 (37% R)
Herpes simplex virus keratitis	6 (17% A)	5 (83% R)	1.0 ± 0.6	10.3 ± 1.4	1.90 ± 0.30	1.50 ± 0.67	19.8 ± 20.8	3 (50% R)	0 (0% R)
Exposure keratopathy	3 (8% A)	2 (66% R)	1.0 ± 1.0	10.2 ± 1.6	2.06 ± 0.05	1.43 ± 0.89	6.6 ± 4.6	1 (33% R)	0 (0% R)
Acanthamoeba keratitis	2 (6% A)	2 (100% R)	1.0/1.0	8.75/10.5	2.10/2.10	NLP/NLP	9/19	0 (0% R)	1 (50% R)
Congenital glaucoma	1 (3% A)	1 (100% R)	1.0	14.0	2.10	2.10	29.4	0 (0% R)	0 (0% R)
Chemical burn	1 (3% A)	0 (0% R)	0	15.0	2.10	1.30	12	1 (100% R)	0 (0% R)
Marginal rheumatoid ulcer	1 (3% A)	0 (0% R)	0	10.0	1.0	1.0	10.8	1 (100% R)	0 (0% R)
Total	35 (100% A)	23 (65% A)	1.2 ± 1.4	10.8 ± 1.7 (8.75–15.0)	1.96 ± 0.23	1.57 ± 0.57	20.2 ± 13.4	12 (34% A)	6 (17% A)

Large-diameter penetrating keratoplasty (LDPKP), best-corrected visual acuity (BCVA) was taken 1 day before the surgery and at last follow-up. Percentages marked with an A relate to the total number of patients (A = all). Percentages marked with R refer to the relative number from each subgroup (R = relative).

for grafts 11.0 mm or larger, the oversize was 1.0 mm. The mean donor endothelial cell count was 1909 ± 334 (min 1163, max 2589, median 1959 cells per mm^2). Sixty percent of grafts with endothelial cell counts of less than 2000 cells per mm^2 were used, but only for emergency PKPs.

After surgery, all eyes received antibiotic drops and steroid drops as standard treatment, and antivirals and antifungal drops were administered individually according to the disease. Systemic treatment included oral methylprednisolone for all patients, and oral antivirals in cases of herpetic keratitis; the dose and tapering were adjusted for each case. When required, drugs were delivered repeatedly (about every 2 days) into the anterior chamber (especially in cases of fungal keratitis). The patients were hospitalized between 3 and 7 days.

Follow-up visits were scheduled for 6 weeks, 6 months, and 1 year after the surgery, with frequent controls (weekly during the first 6 weeks, later every month) by their ophthalmologists or immediately in emergency cases.

Informed consent was obtained from all donors as well as from all patients included in this report on clinical cornea transplantation. The Ethics Committee has ruled that approval was not required for this retrospective study with anonymized data.

Results

Of the 27 included patients, 14 were men and 13 were women. The mean age at the time of the surgery was 62 ± 22 years and the mean corneal graft diameter was 10.8 ± 1.7 (min 8.75, max 15.0) mm. Of the group, 23 eyes (65% absolute) had at least 1 previous PKP (mean graft size, 9.2 ± 1.6 mm), and the average number of previous PKPs was 1.2 ± 1.4 (0–4). The mean time between a previous PKP and the current LDPKP was 17.2 ± 22.8 months. Two patients needed a repeat LDPKP, and three patients needed more than one repeat LDPKP. In total, 35 LDPKPs were performed.

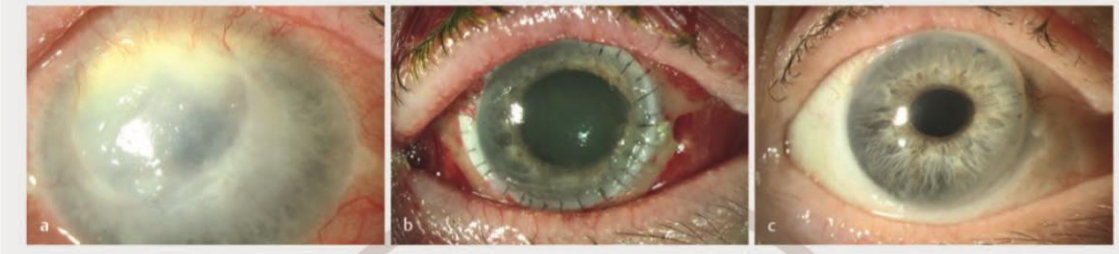
The mean follow-up period was 20.2 ± 13.4 months. Before surgery, the mean BCVA was 1.96 ± 0.23 logMAR; after surgery, it was 1.57 ± 0.57 logMAR. Twelve grafts (35% absolute) remained clear until the last follow-up, but twenty-three grafts (65%) had either disease recurrence or corneal decompensation. Six eyes (17% absolute) were enucleated, five of them because of endophthalmitis (two fungal, three bacterial) and one because of painful refractory ocular hypotony with retinal and persistent choroidal detachment (visual acuity was no light perception after two PKPs for Acanthamoeba keratitis).

Infectious keratitis (fungal, bacterial, herpetic, and Acanthamoeba) represented 83% of the indications. The other 17% included cases of exposure keratopathy (n = 3), congenital glaucoma (n = 1), chemical burn with small perforation (n = 1), and marginal rheumatoid ulcer (n = 1). ▸ **Table 1** summarizes the preoperative data and postoperative outcomes.

Fungal keratitis

Thirteen LDPKPs (nine patients) were performed because of fungal keratitis. Eight of the thirteen eyes (61%) had at least one previous PKP, with a mean time of 13 ± 22 months (1–66 months) between the previous PKP and present LDPKP. The mean corneal graft diameter was 11.0 ± 1.3 mm. Mean BCVA before surgery was 1.96 ± 0.17 logMAR, and mean BCVA at last follow-up (mean

3.3 Publication 3



▸ **Fig. 1** **a** Fusarium fungal keratitis (visual acuity was hand motion). **b** Four days after 12-mm LDPKP (visual acuity 20/630). **c** Eighteen months after surgery, the graft is clear (BCVA 20/63; + 1.75–10.75 × 40)

follow-up, 11 ± 8 months) was 1.69 ± 0.46 logMAR. Five fungal keratitis eyes (38%) required a repeat PKP.

Three fungal keratitis eyes (23%) remained with a clear transplant until the last visit. In nine cases, Fusarium species were the causal agent, as confirmed by microbiology from the excised cornea (▸ **Fig. 1**).

Scedosporium apiospermum was found as the causative agent in only one case, confirmed by biopsy. Three cases were diagnosed as fungal keratitis because clinical findings were negative on biopsy for fungal, herpes simplex virus, or bacterial pathogens.

Prior to surgery, 11 eyes had hypopyon. Eight eyes had received steroid drops prior to the first consultation in our department. Three surgeries were performed as an emergency because of perforated ulcers in this fungal group. In four cases, the lens (one of them with simultaneous IOL) was removed during the LDPKP. All eyes received injections of antifungals into the anterior chamber (amphotericin B and voriconazole) and underwent anterior vitrectomy. One eye also required a posterior vitrectomy because of sonographic signs of endophthalmitis. Two eyes in this group had a history of herpes simplex keratitis [11], and two eyes (15%) required enucleation because of fungal endophthalmitis.

Bacterial keratitis

Eight eyes (six patients) had the procedure because of bacterial keratitis. Five of these eight eyes (62%) had at least one previous PKP, with a mean time between the previous PKP and the present LDPKP of 2 ± 2 (1–6) months. The mean corneal graft size was 10.6 ± 2.0 mm. Prior to surgery, mean BCVA was 2.02 ± 0.70 logMAR, and at last follow-up, it was 1.53 ± 0.70 logMAR.

The mean follow-up time was 11 ± 15 months. Three bacterial keratitis eyes (37%) remained with a clear transplant until the last visit. Two eyes (26%) required a repeat PKP. Three bacterial keratitis eyes (37%) required enucleation because of bacterial endophthalmitis.

Biopsy-confirmed pathogens were *Staphylococcus epidermidis* (n = 2), *Staphylococcus aureus* (n = 2), *Streptococcus pneumoniae* (n = 1), and *Streptococcus anginosus* (n = 1). In two eyes, a biopsy of the excised cornea revealed no pathogens, but in one of these patients, the contact lens was positive for alpha-hemolytic streptococcus.

From the enucleated eyes, only one biopsy was positive for gram (+) bacteria. In the other two biopsies, no pathogens were found.

Herpetic keratitis

Six LDPKPs (five patients) were performed because of herpetic keratitis. Five of the six eyes (83%) had at least one previous PKP, with a mean time from the previous PKP to the present LDPKP of 54 ± 21 months (41–79 months). Mean corneal graft size was 10.3 ± 1.4 mm, and mean BCVA was 1.90 ± 0.30 logMAR before surgery and 1.50 ± 0.67 logMAR at last follow-up. Only one herpetic keratitis eye (16%) underwent a new PKP after the LDPKP, although in two other eyes, another procedure was recommended but not performed.

The mean follow-up period was 20 ± 20 months. Three herpetic keratitis eyes (50%) remained with a clear transplant until the last visit. In the other cases, one patient underwent a repeat LDPKP, and in two more cases, another regular size PKP was recommended [12]. All eyes had a diagnosis of stromal necrotizing keratitis, and in five of them, the LDPKP was performed as an emergency PKP because of a perforated ulcer. In this group, no enucleation had to be performed.

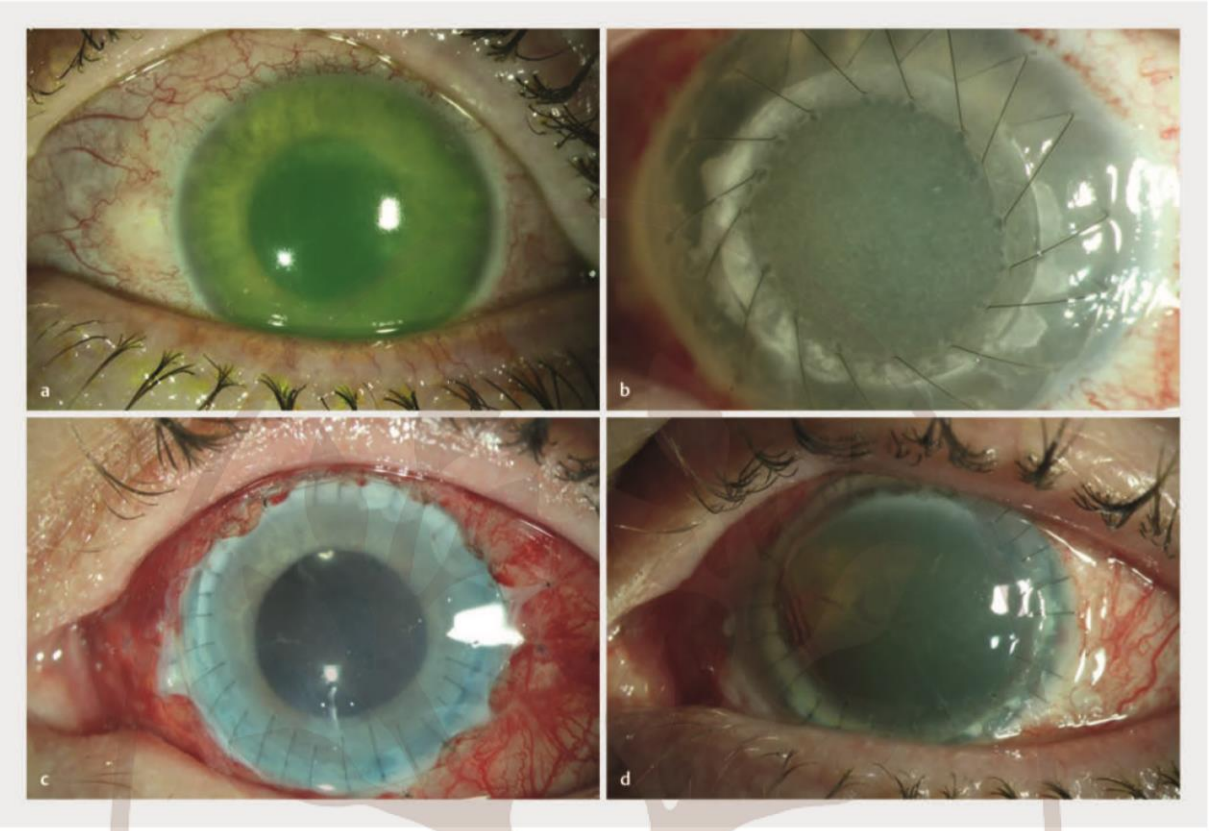
Exposure keratopathy

Three LDPKPs (two patients) were performed because of exposure keratopathy. Two of the three eyes (67%) had at least one previous PKP, with 5 ± 5 months between the previous PKP and present LDPKP. In this group, the mean corneal graft diameter was 10.2 ± 1.6 mm. Before surgery, the mean BCVA was 2.06 ± 0.05 logMAR, and at last follow-up, it was 1.43 ± 0.89 logMAR. One exposure keratopathy eye (33%) needed a new PKP 6 weeks after the LDPKP.

The mean follow-up time was 7 ± 4 months. One eye (33%) remained with a clear transplant until the last visit. In this group, no enucleation had to be performed.

Acanthamoeba keratitis

Two LDPKPs (two patients) were performed because of Acanthamoeba keratitis. Both eyes (100%) had at least one previous PKP, with 1 month and 16 months, respectively, between the previous PKP and the LDPKP. The corneal graft diameter was 8.75 mm



▶ **Fig. 2** **a** Acanthamoeba keratitis (BCVA 20/100; + 2.00–1.75 × 89). **b** One month after an 8.0-mm graft PKP (visual acuity was hand motion). **c** Five days after a 10.5 mm graft LDPKP (no light perception). **d** Eight months after LDPKP (no light perception); the painful eye was finally enucleated 9 months after LDPKP.

in one eye and 10.5 mm in the other eye. The BCVA before surgery was 2.10 logMAR in both eyes. At last follow-up, neither eye had light perception.

The mean follow-up time was 9 months in one eye and 19 months in the other. In both eyes, the diagnosis was confirmed by biopsy.

One Acanthamoeba keratitis eye (50%) required enucleation because of retinal and choroidal detachment associated with refractory hypotension and severe pain. Serial histopathological sections displayed that the enucleated eye was negative for Acanthamoeba trophozoites and cysts (▶ **Fig. 2**) [13].

Other pathologies

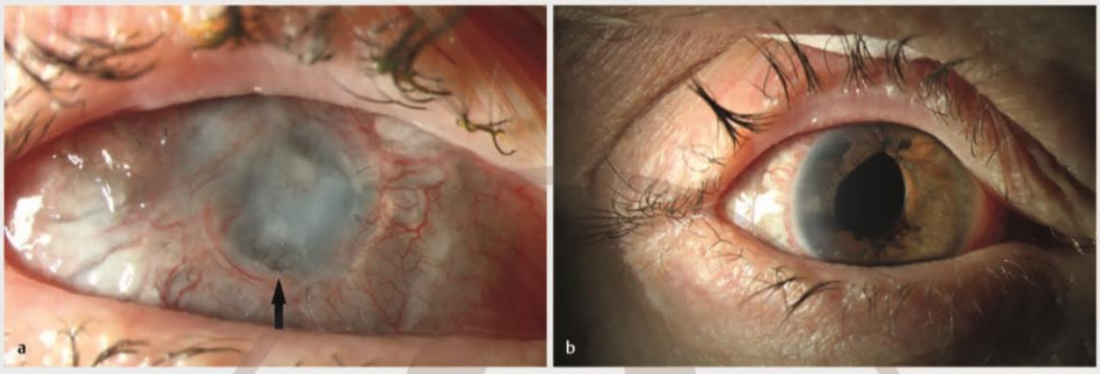
In three cases in which LDPKP was performed, the diagnoses were singular:

- One involved a 10-mm graft keratoplasty in a patient with marginal rheumatoid ulcer, without history of previous transplantation. The follow-up period was 11 months. BCVA before the LDPKP and at last follow-up remained unchanged at 1.0 logMAR. At the last follow-up, the graft remained clear.
- A second case involved a 14-mm graft sclerokeratoplasty in a patient with angle closure, iris tamponade, and previous PKP for congenital glaucoma. Visual acuity before the surgery was 2.1 logMAR, and after 30 months, it was 2.1 logMAR. Because of corneal decompensation, a new 6.5-mm PKP was performed.
- The third singular case involved a 15-mm graft sclerokeratoplasty with lens extraction, permanent lateral tarsorrhaphy, and simultaneous amniotic membrane as a patch in a patient with a history of chemical burn 30 years previously, with a small corneal perforation at 6 o'clock. The BCVA was 2.1 logMAR before the surgery; at last follow-up in our department (10 weeks), it was 1.3 logMAR with a clear transplant (▶ **Fig. 3**). The last follow-up from the patient with the regular ophthalmologist was 12 months after the surgery, and the transplant status and BCVA remained unchanged.

Discussion

Lamellar keratoplasties are becoming more popular, but some situations remain in which a PKP is the only way to manage severe corneal disease, especially in complicated infection (predominantly fungal) cases [3]. In our department, one of the three most active corneal transplantation centers in Germany, PKP remains

3.3 Publication 3



▶ **Fig. 3** **a** 360-degree conjunctivalization of the cornea following chemical burn and small perforation at 6 o'clock (arrow; visual acuity was light perception). **b** Ten weeks after a 15-mm LDPKP lens removal and permanent lateral tarsorrhaphy (BCVA 20/400; + 9.75–0.75 × 150).

the most frequent type of keratoplasty, because ours is a tertiary referral center treating highly complex cases [2]. Many of our patients have undergone at least one previous PKP or been treated elsewhere with conservative therapy without improvement of the disease [14].

Previous authors have suggested that LDPKPs be recommended only in cases of infections or perforations, with a worse prognosis than smaller transplantations [9]. In 2018, Jain et al. published their experience with LDPKP in 28 patients with hopeless microbial keratitis, for which more than one ophthalmologist advised evisceration. BCVA before surgery was poor, and at last the follow-up was 1.0 logMAR or better in half of the patients; only two patients required evisceration because of endophthalmitis. These results are better than those previously reported in such patients, although the follow-up was only 3 months [15].

In our study, infections represented 83% (29 eyes) of the cases; out of these, 31% (9 eyes) had a perforation requiring an emergency keratoplasty, 68% (20 eyes) eyes had undergone a previous PKP, and only 17% (5 eyes) achieved a BCVA of 1.0 logMAR or better at last follow-up.

Fungal keratitis cases made up the largest group in our study at 37% of all cases but represented 45% of the infectious keratitis group. Fungal keratitis is one of the most severe eye diseases worldwide and can lead to blindness. For uncontrollable infections, a surgical approach is required [11, 16]. The prognosis for disease recurrence after keratoplasty is influenced by factors such as misdiagnosis, previous steroid treatment, presence of hypopyon, corneal perforation, and involvement of the limbus or the lens. Fungal recurrence after PKP is a serious surgical complication, and misdiagnosed patients who receive steroids before transplantation have a greater likelihood of recurrence [17].

In 2001, Xie et al. reported their results in the treatment of fungal keratitis in which 64 patients underwent a PKP with a diameter larger than 8.5 mm. Most of these patients had allograft immune reactions that were successfully treated. In recurrent infections that were too large to be removed by keratoplasty and endophthalmitis, enucleation was performed [18]. One year later, this group reported the use of lamellar keratoplasty as a good option for treating fungal keratitis in which the endothelium has not yet been infected, with fewer complications than PKP [19].

In our department, we do clearly advise against choosing deep lamellar keratoplasty in patients with fungal keratitis because of typically full-depth corneal involvement at the time of (not rarely delayed) presentation. The presence of Fusarium solani, hypopyon, previous use of steroid drops, and emergency keratoplasties for corneal perforations were the identifiable high-risk characteristics that may have contributed to the poor outcomes in the present study.

Bacterial keratitis represented a second frequent cause for a LDPKP in our department, at 22% of all cases. Half of these patients had a clear graft at the last follow-up. The other half required an enucleation because of bacterial endophthalmitis. Of the patients who required enucleation, all the LDPKPs were performed as emergency procedures because of perforations. Keratoplasties performed for acute microbial keratitis are associated with higher complication rates and lower graft survival compared to keratoplasty after ulcer resolution. Nevertheless, some indications for emergency keratoplasties in patients with microbial keratitis include corneal perforations, uncontrolled progression of the infiltrates, and limbal involvement with impending scleritis [20].

Eyes with herpetic eye disease typically receive a normal size keratoplasty in the quiet interval after resolution of the infection and inflammation [12]. In cases of deep corneal ulcers, multilayer amniotic membrane transplantation (as "sandwich" i.e. combination of (multilayer) graft(s) and patch) is recommended first to prevent perforation and subsequently to avoid an emergency PKP [21]. In the present study, herpes simplex keratitis was the third common LDPKP indication (17%). In this condition, the goal for the corneal transplantation includes either visual improvement or re-establishment of the integrity of the eye [22]. Perforated eyes need immediate treatment, and large perforations re-

quire a PKP [23]. In cases of emergency PKP, the prognosis is worse than in elective surgery [12,22]. In the current cohort, emergency LDPKP in herpetic keratitis was performed because of corneal perforation in 5 out of 6 eyes.

Only two eyes required LDPKP because of Acanthamoeba keratitis, and the role of corneal transplantation is controversial in these cases. Patients with the best outcomes are those undergoing keratoplasties after 3 months free of infection without treatment, but even these patients may experience recurrences [24,25]. Multiple therapeutic grafts may be required in medically unresponsive cases of Acanthamoeba keratitis with guarded visual prognosis [26]. Keratoplasties in patients receiving effective medical therapy have lower recurrence rates but with poor anatomic and visual outcomes [27]. One of the biggest problems in treatment of Acanthamoeba keratitis relies on confusing the disease with another type of keratitis and the use of steroids prior to a correct diagnosis. In cases of Acanthamoeba keratitis with rapid dissemination in the direction of the limbus, an emergency PKP is recommended [28,29]. Our results agree with previous reports because both patients had recurrence of the disease and ended with non–light perception eyes. One of the two eyes required enucleation because of hypotony refractive to treatment associated with retinal and choroidal detachment. The pathology results of the enucleated eye showed no evidence of Acanthamoeba trophozoites or cysts. These findings lead us to support that reactive uveitis with retinal vasculitis and scleritis as an ocular end stage of Acanthamoeba keratitis contributes to the poor prognosis [13]. However, these disastrous outcomes in the present series are not representative because most cases of transplantation for Acanthamoeba were treated with normal-size grafts with acceptable results as long as the course of a therapy-resistant disease was no longer than five months [30].

In the other 17% of the LDPKPs, the indications were exposure keratopathy (two patients, three eyes), marginal rheumatoid ulcer (one patient), history of chemical burn with small perforation (one patient), and congenital glaucoma (one patient). One sclerokeratoplasty was performed in the patient with a history of chemical burn 30 years before, with total limbal insufficiency and a small corneal perforation. In these situations, there are two treatment options: sclerokeratoplasty or normal size keratoplasty in combination with or subsequent to limbal stem cell transplantation [31]. In this case, a sclerokeratoplasty with simultaneous amniotic membrane transplantation as a patch and permanent lateral tarsorrhaphy were performed. At 12 months after the surgery, the transplant remained clear.

Conclusions

Complex cases of infectious keratitis unresponsive to conservative management and with a history of previous transplants require LDPKP to remove the complete pathology and preserve the integrity of the eye. The visual outcomes are poor not only because of the well-known risks of large-diameter keratoplasties but also because of the consequences of the infectious disease itself. Finally, 17% of these eyes required enucleation. This knowledge is important for adequate counseling of these patient preoperatively. In contrast, 8.5 mm keratoplasties that are performed for high astigmatism management after PKP are also considered LDPKPs in the literature, but they represent a completely different clinical scenario with highly favorable prospects [4].

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Conflict of Interest

The authors declare that they have no conflict of interest.

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3.3 Publication 3

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4. Conclusions

We can conclude that the 8.5/8.6-mm excimer laser-assisted PKP is an excellent treatment option in cases of ectatic disorders for which an 8.0-mm graft seems too small, and for corneal scars that require larger grafts to completely remove the lesion. All the patients with ectatic disorders (n=30) in our first study, exhibited a clear graft until the last follow-up. Additionally, 8.5/8.6-mm excimer laser-assisted PKP represents a good treatment option in cases of highly irregular astigmatism, with such cases showing significant improvement of BCVA due to increased corneal regularity. All the patients with high irregular astigmatism (n=30) in our first study also showed clear grafts until the last follow-up.

Nevertheless, we also found that PKPs bigger than 8.5/8.6mm performed in patients with complex cases of infectious keratitis unresponsive to conservative management and with a history of previous transplants, the visual outcomes were poor not only because of the well-known risks of large-diameter keratoplasties but also because of the consequences of the infectious disease itself. 17% (n=6) of eyes included in the third study required enucleation. This knowledge is important for adequate counseling of these patients preoperatively.

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7. Curriculum Vitae

The curriculum vitae was removed from the electronic version of the doctoral thesis for reasons of data protection.