

## ORIGINAL ARTICLE



# Long-term outcomes of therapeutic penetrating keratoplasty versus elective penetrating keratoplasty in a tertiary care center in Israel

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Elective keratoplasty, hot graft, penetrating keratoplasty, therapeutic keratoplasty

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doi: 10.15713/ins.clever.43**Abstract****Purpose:** The purpose of the study was to compare the results of therapeutic keratoplasty (TK) with those of elective penetrating keratoplasty (PK).**Materials and Methods:** A retrospective case–control institutional study design was used. The medical records of patients that underwent full thickness or lamellar keratoplasty between 1/2008 and 12/2015 in Rabin Medical Center (Petach Tikva, Israel) were evaluated. The study group included eyes which had TK. The control group included eyes which had PK during the study period. Outcome measures included demographic details, indication for TK, follow-up time, intraoperative and post-operative complications, the need for additional surgeries, best-corrected visual acuity (BCVA), and the presence of a clear graft at last documented visit.**Results:** Out of 1094 keratoplasties performed in the study period, 17 (1.55%) were therapeutic penetrating keratoplasties. The control group consisted of 240 consecutive penetrating keratoplasties. Indications for TK were severe infections (14 eyes, 82.4%) and sterile perforations (3 eyes, 17.6%). In 9/17 (52.9%) TK eyes, there was a preexisting penetrating corneal graft. Twelve corneas were perforated at the time of surgery (12/17–70.6%). Eight infected corneas were perforated at the time of surgery (8/14–57.1%). No intraoperative complications were noted for any patient. There were no differences in age and follow-up period between the groups. Primary failure rates were higher in the study group (29.4% vs. 14.6%,  $P = 0.15$ ) and fewer eyes in the study group had clear cornea at last documented visit (66.7% vs. 77.5%,  $P = 0.48$ ). Persistent epithelial defects and glaucoma were more common in the study group (47.1% vs. 5.0%,  $P < 0.0001$  and 47.1% vs. 17.1%,  $P = 0.006$ , respectively), as were the need for additional surgeries (64.7% vs. 18.7%,  $P = 0.0001$ ). BCVA on last visit was worse in the study group with only 11.8% having 6/45 visual acuity or better versus 41.7% in the control group ( $P = 0.02$ ).**Conclusions:** Results of TK are inferior to those of elective PK. However, the primary purposes of TK, namely, saving the globe and maintaining useful visual acuity can be achieved in most cases. The increased complication rate and the probable need for additional procedures should be discussed with the patient.**Introduction**

Therapeutic keratoplasty (TK) is a time-honored, last-resort procedure aimed at preventing irreversible loss of vision and/or globe integrity due to severe corneal inflammation.<sup>[1,2]</sup>

The main indications for TK include progressive infectious keratitis refractory to medical treatment, with impending scleral extension or perforation, and sterile impending or frank corneal perforation caused by immunological diseases.<sup>[2,3]</sup>

Outcomes of TK were reported to be less favorable than those of elective penetrating keratoplasty (PK) and this procedure was associated with a higher incidence of allograft rejection and graft failure and with guarded visual outcomes.<sup>[2-5]</sup> Furthermore, the incidence of post-operative complications such as cataract, synechiae, glaucoma, wound dehiscence, recurrent perforation, and uveitis was reported to be increased.<sup>[1-6]</sup> This difference is explained by the presence of active inflammation of the recipient cornea and the anterior chamber and by the use of large or eccentric grafts.<sup>[1-5]</sup>

As in recent years, surgical techniques have improved, as well as our ability to treat post-operative complications,<sup>[1,3,7]</sup> we aimed at comparing again the clinical results of TK with those of elective PK done recently in our institution, a university-affiliated hospital, which currently performs the largest number of keratoplasties in Israel, amounting to 150 in a year.

## Materials and Methods

In this retrospective case-control study, the medical records of patients that underwent full thickness or lamellar keratoplasty between 1/2008 and 12/2015 in Rabin Medical Center (Petach Tikva, Israel) were evaluated. The study group included eyes which had TK during the study period, and the control group included 240 consecutive cases of elective PK done at January 2008 and on. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Rabin Medical Center.

### Data collection

Outcome measures included demographic details, indication for TK, follow-up time, intraoperative and post-operative complications, and specifically, primary graft failure, graft rejection episodes, persistent epithelial defects, recurrent infections, glaucoma, the need for additional surgeries, best-corrected visual acuity (BCVA), and the presence of a clear graft at last documented visit.

### Statistical analysis

All data collected in the study were entered into an electronic database through Microsoft Excel 2007 (Microsoft Corp., Redmond, WA). Data were analyzed with MedCalc version 12.7.1.0 (MedCalc Software, Mariakerke, Belgium). For the analysis of quantitative measures, Student's *t*-test was used. Fisher's exact test was used for the analysis of categorical variables.  $P < 0.05$  was considered statistically significant.

Following the record screening and identification of the study group population, the minimal sample size of the control group was chosen as such that could find a difference of 30% complication rate between the groups with a power of 80% and significance level  $\leq 0.05$ .

## Results

A total of 1094 corneal transplants were performed from January 2008 through December 2015 in our institution. Nineteen eyes of 19 patients (1.73%) were identified as TK. Two surgeries that were performed urgently for the treatment of corneal perforation were not PK. One eye had Boston keratoprosthesis transplantation, and the other had tectonic Descemet's stripping automated endothelial keratoplasty (DSAEK) described elsewhere.<sup>[8]</sup> These two eyes were excluded from the study group, leaving 17 eyes of 17 patients, which are 1.55% of all cases.

Twelve patients (70.5%) in the study group were female compared to 89/240 (37.1%) in the control group ( $P = 0.009$ ). The mean age of patients in the study group was  $62.0 \pm 19.0$  years (range 21–87) compared with  $54.8 \pm 22.6$  years in the control group ( $P = 0.08$ ). The mean follow-up time was similar between the study and the control groups ( $4.6 \pm 2.2$  years vs.  $4.7 \pm 1.4$ ,  $P = 0.41$ ).

Indications for TK included uncontrollable infectious keratitis in 14/17 eyes (82.4%), toxic epidermal necrolysis causing corneal perforation (two eyes), and corneal perforation caused by rheumatoid arthritis (one eye). In 9/17 (52.9%) TK eyes, there was a preexisting penetrating corneal graft. Twelve corneas were perforated at the time of surgery (12/17–70.6%). Eight infected corneas were perforated before surgery (8/14–57.1%). No intraoperative complications were noted for any patient. Cultures were positive in 12/14 (85.7%) of presumably infected corneas. Culture results included pneumococcus (two eyes), pseudomonas, streptococcus viridans, *Kocuria rosea*, *Acanthamoeba*, *Candida*, *Penicillium*, and *Aspergillus* (one eye each). In three eyes, herpes simplex virus was detected by polymerase chain reaction. Two presumably infected corneas were culture negative.

Demographic details and clinical outcomes of both groups are described in Table 1.

Briefly, primary graft failure was more common in the study group (29.4% vs. 14.6%,  $P = 0.15$ ). Fewer eyes in the study group showed clear cornea at last documented visit (66.7% vs. 77.5%,  $P = 0.48$ ). Kaplan–Meier survival curves for both groups are shown in Figure 1.

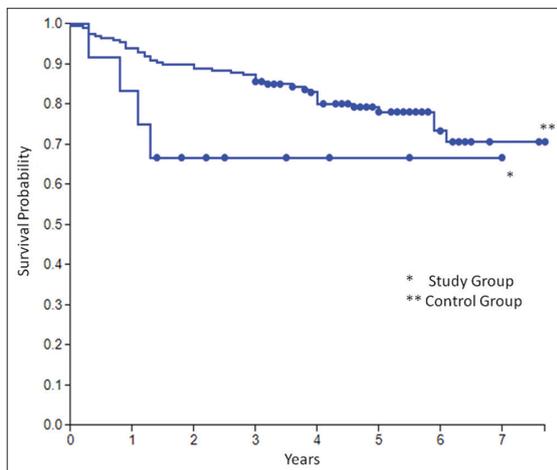
Graft rejection episodes were less common in the study group (2/17–11.7% vs. 52/240–21.7%,  $P = 0.53$ ). Both episodes seen in the study group were reversible with medical treatment.

Post-operative persistent epithelial defects were significantly more frequent in the study group (47.1% vs. 5.0%,  $p < 0.0001$ ) as well as post-operative glaucoma (47.1% vs. 17.1%,  $P = 0.006$ ). However, only one patient in the study group and six eyes in the control group required glaucoma surgery (5.9% vs. 2.5%,  $P = 0.38$ ).

Post-operative infections occurred in four patients in the TK group (23.5%) versus 22 eyes (9.2%) in the EK ( $P = 0.06$ ). All four cases occurred in eyes that were primarily operated for uncontrolled infections. Three of these infections were caused by a different pathogen than the primary infection

**Table 1:** Demographics details and clinical outcomes of patients undergoing therapeutic keratoplasty versus patients undergoing elective penetrating keratoplasty

	Therapeutic keratoplasty	Elective keratoplasty	P
Number of eyes	17	240	
Demographic details			
Age (years)	62.0±19.0	54.8±22.6	0.08
Sex (% of females)	12 (70.5%)	89 (37.1%)	0.009
Follow-up (years)	4.6±2.2	4.7±1.4	0.41
Best-corrected visual acuity on last visit			
No light perception	4 (23.5%)	8 (3.3%)	0.0047
Light perception-finger count	7 (41.2%)	43 (17.9%)	0.028
1/9–6/60	4 (23.5%)	77 (32.1%)	0.594
6/45 or better	2 (11.7%)	100 (41.7%)	0.0188
No light perception	4 (23.5%)	8 (3.3%)	0.0047
Post-operative complications (number of eyes)			
Primary graft failure	5 (29.4%)	35 (14.6%)	0.15
Graft rejection	2 (11.7%)	52 (21.7%)	0.53
Clear cornea at last visit	11(64.7%)	186 (77.5%)	0.48
Persistent epithelial defect	8 (47.1%)	12 (5.0%)	<0.0001
Glaucoma	8 (47.1%)	41 (17.1%)	0.006
Infectious keratitis	4 (23.5%)	22 (9.2%)	0.06
Additional surgeries	11 (64.7%)	45 (18.7%)	0.0001

**Figure 1:** Kaplan–Meier survival curves for patients undergoing therapeutic therapy versus patients undergoing elective penetrating keratoplasty

(*Serratia*, *Streptococcus hemolyticus*, and *Candida parapsilosis*) while a single case had recurrence of the same pathogen (*Penicillium*).

TK was associated with increased need for additional surgery (11/17–64.7% vs. 45/240 18.7%,  $P = 0.0001$ ). Procedures done in the study group included wound dehiscence repairs, suture revisions, cataract surgeries, amniotic membrane transplants, and eviscerations (two each), tarsorrhaphy, trabeculectomy, pars

plana vitrectomy with silicone oil injection, and one drainage of choroidal detachment (one each).

Procedures done in the control group included 8 relaxing incisions, 7 suture revisions, 7 repairs of wound dehiscence, 6 glaucoma surgeries, 5 tarsorrhaphies, 5 cataract surgeries, 5 pars plana vitrectomies, one entropion surgery, and one case of Nd:YAG laser application on retained Descemet's membrane.

Final BCVA varied tremendously among patients in the study group, as 4 patients (23.5%) had no light perception (NLP), 3 (17.6%) had light perception (LP), 3 (17.6%) perceived hand motion, 1 (5.9%) was counting fingers, 4 (23.5%) had BCVA ranging between 1/9 and 6/60, and 2 (11.8%) had 6/45 or better. The control group showed more favorable results with only 18 patients (7.5%) having final BCVA of LP or worse (vs. 41.1% in the study group,  $P < 0.0001$ ) and 100 patients (41.7%) having final BCVA of 6/45 or better (vs. 11.8%,  $P = 0.02$ ). For 12 patients in the control group, BCVA at final visit was not available.

## Discussion

TK comprised <2% of all keratoplasties done in our institution, with a rate of about two cases per year. This is consistent with the previous reports from developed countries in which TK was uncommon.<sup>[7,9,10]</sup>

Notably, more than half of the TK cases were performed on preexisting penetrating corneal grafts. PK grafts are prone to infection from many reasons including chronic steroid

treatment, retained sutures, and ocular surface abnormalities associated with PK.

TK is considered more technically challenging than elective PK, and it is associated with the use of large or eccentric grafts, macerated recipient tissue, difficult trephination when perforation is present, hyphema, need of synechiolysis, anterior vitrectomy, etc.<sup>[1,3,6,11]</sup> Despite this, no intraoperative complications were noted in any of the surgical reports in the study group. It might be that there were minor complications that were not recorded in the surgical notes. An access to the surgical videos could have provided us with a more complete picture of the possible challenges posed by these cases.

This study showed a great difference in the rate of primary graft failure between the groups with nearly 30% failure rate in the study group, more than double than the control group. The high rate of primary failure in the current study is in line with the series described by Hanada *et al.*<sup>[1]</sup> However, no data regarding primary failure rates could be found in other studies<sup>[2,5,6,11,12]</sup> as it was embedded within more general information regarding graft failure. This high rate could be explained by the severe intraocular inflammatory response before and after the operation as well as the longer duration of the operation and intraoperative graft manipulations. Although for emergent TK, a graft of lower quality can be used, only 3 grafts (17.6%) used in this series had a pre-operative cell count of <2000 cells/mm<sup>2</sup>.

Surprisingly, the rate of TK grafts remaining clear at last follow-up visit was almost 70% and was similar to the corresponding rate in the control group (out of all grafts that did not fail primarily). This number is in accordance with the previous large series<sup>[5,7,12]</sup> that showed slight differences attributed to different follow-up times. This result is encouraging and supporting the general notion that every effort should be made to save the globe even in the face of a devastating infection or sterile perforation. Moreover, with the advent of endothelial keratoplasty, some eyes with primary or late failure can regain sustainable corneal transparency, as reported by Chaurasia *et al.*<sup>[13]</sup> and Ramamurthy *et al.*<sup>[14]</sup>

The most frequent post-operative complications in the study group were persistent epithelial defect and glaucoma (66.7% each), both significantly more common than in the control group. These rates are substantially higher than described in other studies with long follow-ups, which described rates of up to 18.8% for persistent epithelial defect and up to 10.5% for glaucoma.<sup>[1,5,7,8]</sup> Our increased rates for these complications might be the result of preexisting glaucoma and ocular surface disease in our patients, most of them transplanted following primary PK. For sterile perforations, a new technique of tectonic DSAEK was recently described by our group.<sup>[8]</sup> This procedure may possibly avoid the worsening of preexisting ocular surface disease by PK.

In contrast to the high rate of clear grafts, the study group demonstrated poor final BCVA that was significantly worse than the control group (11.8% with BCVA of 6/45 or better vs. 41.7%, respectively,  $P = 0.02$ ). However, this rate was also lower than reported in other studies, as Anshu *et al.*<sup>[12]</sup> reported 20% of the patients with final BCVA of 6/9 or better, Ti *et al.*<sup>[7]</sup>

reported 58% with at least 6/60. Since TK patients present a very heterogeneous group, it is hard to draw any conclusion from these data, but it might be that performing TK earlier during the disease course has resulted in better visual outcomes.

## Conclusions

This study showed that results of TK are guarded in comparison to those of elective PK, but that in most cases, the surgery served its primary purpose of saving the globe and also provided useful vision in a considerable number of eyes. As following TK, most patients will require additional interventions, the need for tight follow-up and possibly, more surgeries, should be discussed with the patient before surgery, and expectations should be tempered accordingly.

## Compliance with ethical standards

### Funding

No funding was procured for this work.

### Conflicts of interest

Yoav Nahum is a paid consultant for Shire PLC and Taro Pharmaceutical Industries.

### Ethical approval

All procedures in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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