Original Article

Outcome of transplanted donor corneas with more than 6 h of death-to-preservation time

Ashik Mohamed, Sunita Chaurasia[1], Prashant Garg[1]

Purpose: In tropical countries, physicians are skeptic in using corneas with death-to-preservation time (DTPT) >6 h, concerns being endothelial cell viability and microbial contamination on prolonged DTPT. The objective of the study was to investigate these concerns by analyzing the outcomes of corneal transplants performed using donor corneas with DTPT >6 h. **Materials and Methods:** The study was a retrospective case series of 65 transplants performed in 2013 with donor corneas that had DTPT >6 h (range, 6.1–9.8 h). The information on donor cornea tissues and the recipient details were collected from the eye bank and the medical records department of our tertiary eye care center. The main outcome measures were slit lamp assessment of the donor corneas, primary graft failure, graft survival, and postoperative adverse reactions, especially infections, if any. **Results:** Median DTPT was 7 h. Forty-four (67.7%) corneas were evaluated as optical grade and 21 (32.3%) were deemed as therapeutic grade; 36 (55.4%) were used for optical indications. There was no relationship between DTPT and the tissue grading of corneas or endothelial cell density. Of the 23 keratoplasties for purely optical indications with a minimum follow-up of 3 months, 15 (65.2%) remained clear whereas 7 (30.4%) failed (mean follow-up 15.1 ± 6.7 months). The causes of failure were primary graft failure (n = 1) and secondary graft failure (n = 6). **Conclusion**: The donor corneas with DTPT 6 h to 10 h can be utilized for optical indications provided that they meet the criteria of tissue acceptance for optical use.

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Keratoplasty is the most commonly performed transplantation procedure worldwide, which has been possible with the advancement in eye banking practices. However, unlike other solid organ transplants, the corneal tissues are retrieved after death. Since degradation of tissues begins after the cessation of circulation which in turn releases cytotoxic substances, it is presumed that with increasing time after death, the quality of donor tissues including corneas will become poorer. Further, the microbial flora continues to change both qualitatively and quantitatively. Therefore, there is a time limit for harvesting donor corneas or eyeballs.[1] Unfortunately, there is a discrepancy in acceptable limits for this death-to-preservation time (DTPT) and some researchers claim that there are no such upper time limits, and as long as certain quality criteria are met, corneas can be used for grafting.[2,3] Bock suggested that corneal excision can be done up to 12 h after death provided the cadaver is refrigerated.[4] Paton permitted an interval of only 5 h after death with provisions being that the eyelids are carefully closed after death, antibiotic drops instilled in the conjunctival sac, and the body refrigerated.[5] Paufique permitted an interval of 24 h but stressed the importance of enucleation within 6 h after death if the above conditions cannot be fulfilled.[6]

There is variability in the weather conditions in some countries with temperature rising as high as 40°C in summer months and dropping down to single digits in winters. One study evaluated the effect of seasonal variations on the viability of corneal tissue in the Indian tropical climate and found that in the hot summer months, the corneas become unsuitable much earlier.[7] The authors recommended that the eyes should be removed within the accepted time limit of 6–12 h after death. In the colder winter months, however, this time interval can be extended even up to 18–24 h as the corneal condition remains satisfactory for a longer time.

The eligibility criteria for the donor corneas, as per the standards of the Eye Bank Association of America, include DTPT ≤12 h if donor body is refrigerated or eyes iced and ≤8 h if not.[8] In contrast to the reports from Western world's eye banks, tropical countries with hot and humid climate adopt 6 h as cutoff for unrefrigerated bodies as a working policy in their eye banks. In developing countries, it was found that majority of the tissues were retrieved within 6 h of death through the cornea retrieval program.[9]

The purpose of our study was to examine the outcomes of transplanted corneas from *in situ* excision in a hospital setting with DTPT >6 h when the deceased was not refrigerated.

Ophthalmic Biophysics, L. V. Prasad Eye Institute, [1]Cornea and Anterior Segment Services, L. V. Prasad Eye Institute, Hyderabad, Telangana, India

Correspondence to: Dr. Sunita Chaurasia, Cornea and Anterior Segment Services, L. V. Prasad Eye Institute, L. V. Prasad Marg, Banjara Hills, Hyderabad - 500 034, Telangana, India. E-mail: sunita@lvpei.org

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Materials and Methods

The approval of the Institutional Review Board was obtained for the study and the research adhered to the tenets of the Declaration of Helsinki. The information on donor cornea tissues and the recipient details were collected from the eye bank and the medical records department of our tertiary eye care center for the year 2013. At our eye bank, the *in situ* excision is performed by trained technicians and the retrieved corneas are preserved in the McCarey-Kaufman (MK) medium, which is a short-term preservation medium. Although the standard practice is to utilize corneas within the DTPT of 6 h as the upper limit, some corneas with DTPT >6 h were utilized as these were graded suitable for transplantation and hence could be analyzed in this study. Details of the time of donor's death were documented from the records of the deceased, and the time from death to excision and preservation into the MK medium were noted from the eye bank records.

The donor corneas were evaluated on slit lamp (SL 115, Carl Zeiss Meditec AG, Jena, Germany) and specular microscope (Eye Bank KeratoAnalyzer, Konan Inc., Hyogo, Japan) to grade the tissues and determine the suitability of transplantation. The slit lamp grading (optical vs. therapeutic grade) of the corneas whose DTPT was >6 h, primary indication of transplants, and adverse events following transplants with these corneas were reviewed retrospectively. Outcome of the optical transplants (optical penetrating keratoplasty [PK] and endothelial keratoplasty [EK]) was analyzed for primary graft failure and long-term graft survival. Few parameters such as donor age, utilization rate, proportions of optical keratoplasty versus therapeutic keratoplasty, and endothelial cell density (ECD) of corneas with DTPT >6 h were compared with those of corneas with DTPT ≤6 h.

The data analysis was performed using the software Origin version 7.0 (OriginLab Corporation, Northampton, MA, USA) and STATA v11.0 (StataCorp LP, College Station, Texas, USA). The continuous data were checked for normality using Shapiro–Wilk test. Descriptive measures included mean and standard deviation for data with normal distribution, whereas those that were not normally distributed were described using median and interquartile range (IQR). Categorical data were described in proportions and compared using Chi-square test. Mann–Whitney U-test (2 groups) and Kruskal–Wallis test (>2 groups) were used for comparisons between nonparametric data. Spearman rank-order correlation was done to assess the relationship between nonparametric variables. Kaplan–Meier survival analysis was performed to compute the probability of graft survival. A $P < 0.05$ was considered statistically significant.

Results

Eye bank statistics – 2013

The total number of corneas retrieved in the year 2013 was 4648, of which 2190 (47.1%) were utilized for transplantation. A total of 1204 transplants were performed at our tertiary eye care center, of which 65 (5.4%) transplants were performed using donor corneas that had DTPT >6 h (upper limit 9.8 h).

Characteristics of donor corneas with death-to-preservation time >6 h

The median DTPT was 7 h (IQR, 6.5–8 h). Based on the standard guidelines of donor cornea evaluation which involves clinical slit lamp examination and specular microscopy,[10] 44 (67.7%) of 65 corneas were evaluated as optical grade and 21 (32.3%) were evaluated as therapeutic grade. There was no relationship between DTPT and the quality grading of corneas into optical and therapeutic ($P = 0.10$) (optical grade corneas: Median DTPT 7.25 h [IQR, 6.5–8 h] vs. therapeutic grade corneas: Median DTPT 6.75 h [IQR, 6.25–7.25 h]). There was no relationship between DTPT and ECD ($P = 0.07$).

Outcomes of optical keratoplasty using donor corneas with death-to-preservation time >6 h

Of the 44 optical grade corneas, 35 (79.6%) were used for optical transplants and 9 (20.4%) were used for therapeutic indications. The median age of the recipient at the time of surgery was 53.2 years (IQR, 29.8–60.7 years). Of the 35 keratoplasties done for purely optical indications (EK and optical PK), 23 (65.7%) had a follow-up duration of at least 3 months, the mean duration being 15.1 ± 6.7 months (3.2–26.5 months). Among these 23 transplants, 15 (65.2%) remained clear whereas 7 (30.4%) failed. Fig. 1 shows the probability of survival of these grafts. The grafts had a 2-year survival rate of 63.8% ± 11.1%. All were secondary graft failures but for one case of primary graft failure, which was a complicated Descemet's stripping EK performed for a complex pseudophakic corneal edema [Table 1]. There were no other primary graft failures. There was a case of interface infection (1.5%), following a Descemet's stripping EK. The mate pair of this donor was used for an optical PK with no adverse event in the postoperative period.

Comparison to donor corneas with death-to-preservation time ≤6 h

Table 2 summarizes the comparison of donor-related characteristics between corneas with DTPT >6 h and ≤6 h. The age of the donors with a DTPT >6 h was slightly younger compared to those with a DTPT ≤6 h. However, there was no difference in the primary indication of corneal transplants. Similar to corneas with DTPT >6 h, there was no relationship between DTPT and ECD ($P = 0.57$) in corneas with DTPT ≤6 h. The utilization rate (number of corneas utilized/number of corneas retrieved) was lower (45.6%) in corneas with DTPT >6 h.

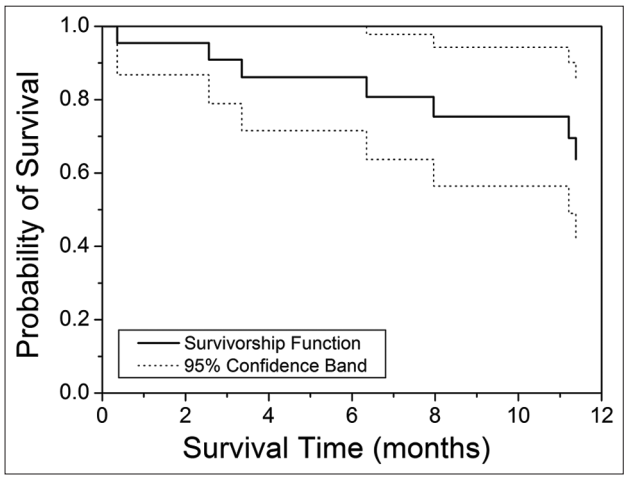

Figure 1: Survival analysis – This figure shows the survival probability of the corneal grafts (death-to-preservation time >6 h: minimum follow-up of 3 months) done for purely optical indications

Table 1: Summary of graft failures

Failed grafts (*n*=7)	Indication for transplant	Surgery performed	Type of graft failure	Cause of graft failure
1	Failed graft	DSAEK	Primary	Secondary to complicated DSAEK
2	Corneal scar	Optical PK	Secondary	Rejection followed by graft infiltrate
3	Corneal scar	Optical PK	Secondary	Rejection followed by graft infiltrate
4	Failed graft	DSAEK	Secondary	Rejection followed by graft infiltrate
5	Failed graft	Optical PK	Secondary	Recurrence of limbal stem cell deficiency in the graft
6	Endotheliitis	DSAEK	Secondary	Recurrence of viral endotheliitis
7	Pseudophakic corneal edema	Optical PK	Secondary	Rejection followed by graft failure

This table summarizes the graft failures, indications of such transplants, and the causes for failure. DSAEK: Descemet's stripping automated endothelial keratoplasty, PK: Penetrating keratoplasty

Table 2: Comparison of donor corneas: Death-to-preservation time >6 h versus death-to-preservation time ≤6 h

Donor parameter	DTPT >6 h (*n*=65)	DTPT ≤6 h (*n*=1139)	*P*
Age (years), median (IQR)	52 (27-69)	57 (40-72)	0.04
Utilization rate	45.6% (95% CI: 40.0%-51.4%)	53.4% (95% CI: 51.9%-54.9%)	0.008
Endothelial cell density (cells/mm^3), median (IQR)	2796.5 (2409-3164)	2624 (2314-2898)	0.02
Primary indications (optical vs. therapeutic)	Optical transplants=36 (55.4%; 95% CI: 42.6%-67.5%) Therapeutic=29 (44.6%; 95% CI: 32.5%-57.4%)	Optical transplants=654 (58.0%; 95% CI: 55.0%-60.9%) Therapeutic=474 (42.0%; 95% CI: 39.1%-45.0%)	0.78

This table summarizes the comparison of donor-related parameters between corneas with DTPT>6 h and those with DTPT≤6 h. CI: Confidence interval, DTPT: Death-to-preservation time, IQR: Interquartile range

Discussion

In this study, we examined the outcomes of corneal transplantations where the donor tissue, after *in situ* excision, had a DTPT of more than 6 h and up to 10 h. Understanding the influence of key donor factors such as DTPT on the outcomes of transplants helps in providing a rationale for the standard functioning of eye banks. Studies have been done to evaluate the relationship between DTPT and the quality of donor tissue where the analysis included all the donor tissues (enucleation and excision).[11] Ranjan *et al*. attributed the good utilization rate of *in situ* excised donor corneal tissues to shorter DTPT (<6 h) in the majority.[9] In another study, DTPT within the range of <5 h–>12 h was shown to be unrelated to the degree of endothelial cell loss, following PK for endothelial disorders.[12] Following eye bank specular microscopy and assessment of endothelial cell morphology, some tissues were found to remain good at longer time (>6 h) after death.[13] Studies that have examined the quality of donor tissues and the outcome of transplants with donor corneas with DTPT >6 h are few.

The statistics at our eye bank for the year 2013 revealed that the donor corneas with DTPT >6 h had a higher ECD than those <6 h, which could probably be due to relatively younger donors in this subset. In addition, the proportion of optical transplants (~57%) performed in both the subsets were equivalent. With the donor corneas with DTPT >6 h (range, 6.1–9.8 h), optical- and therapeutic-graded tissues had comparable DTPTs, showing that DTPT does not impact the quality grading significantly. The cell density of the corneal endothelium of the *in situ* excised tissues was not found to be related to DTPT in our study. The long-term outcome of optical transplants with these corneas had a survival rate of ~64% at the end of 2 years, following the surgery. The success of optical keratoplasty with these corneas at 2 years follow-up was found to be somewhat better compared to our historical control data (success rate of 59% at 1 year from an earlier recent study on the outcomes of all optical transplants in the year 2012: Unpublished data). Except one case (1.5%) of interface infiltrate where it could not be ascertained that it was donor-related infection, no other adverse event is noted.

Medical standards usually recommend minimizing the time between death and cornea removal. It is intuitive to understand that, following death, the metabolic processes cease to exist and provide a healthy environment to the donor endothelium. The tissue should ideally be retrieved quickly and transferred into a healthy medium. However, the delay in recovery is a practical reality in some instances and because workforce and serological testing costs exist for all tissues harvested (regardless of whether or not the tissue is utilized), the economic ramifications of discarding a tissue are not small. Discarding all such corneas with DTPT more than 6 h may lead to a shortage of tissues suitable for surgery, particularly in developing countries.[11,13] Although every possible measure should be taken to facilitate the recovery and preservation process, the decision for utilization for clinical use of such corneas (with DTPT up to 10 h) can be made if they meet the criteria of tissue acceptance for optical use on the basis of standard guidelines of donor cornea evaluation.

Conclusion

In summary, the donor corneas with DTPT 6 h to 10 h can be utilized for optical indications provided that they meet the criteria of tissue acceptance for optical use.

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Conflicts of interest

There are no conflicts of interest.

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