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Cost-effectiveness of Descemet stripping automated endothelial keratoplasty versus penetrating keratoplasty in patients with endothelial dysfunction in India

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Purpose: The aim of this study was to compare the cost-effectiveness and perform cost-utility analysis of Descemet stripping automated endothelial keratoplasty (DSAEK) vs. penetrating keratoplasty (PK) in Indian population. **Methods:** This was an institutional, ambispective, observational study. Patients who underwent PK or DSAEK for endothelial dysfunction were included and followed up for 2 years; those with other ocular comorbidities were excluded. The analysis was performed from the patient's perspective receiving subsidized treatment at a tertiary care hospital. Detailed history, ophthalmic examination, total expenditure by patient, and clinical outcomes were recorded. The main outcome measures were best spectacle-corrected visual acuity (BSCVA), graft survival (Kaplan–Meier survival estimates), incremental cost-effectiveness ratio (ICER), and incremental cost-utility ratio (ICUR). Utility values were based on quality-adjusted life years (QALYs) associated with visual acuity outcomes. Statistical analysis was performed using SPSS software package, version 12.1; a value of $P < 0.05$ was considered statistically significant. **Results:** A total of 120 patients (PK: 60, DSAEK: 60) were included. At 2 years, for a similar logMAR BSCVA, [PK (0.32 ± 0.02), DSAEK (0.25 ± 0.02); $P = 0.078$], the overall cost for PK (13511.1 ± 803.3 INR) was significantly more than DSAEK (11092.9 ± 492.1 INR) (difference = 1952.6 INR; $P = 0.01$). ICER of DSAEK relative to PK was –39,052 INR for improvement in 1 logMAR unit BSCVA. ICUR of DSAEK relative to PK was –1,95,260 INR for improvement in 1 QALY. **Conclusion:** DSAEK was more cost-effective than PK in patients with endothelial dysfunction at 2 years.

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Safety and efficacy are the most extensively studied parameters for any surgical procedure, and the same holds true for cornea transplantation. Despite being the most commonly performed and the most successful solid organ transplant, there are few practical limitations that hinder its large-scale implementation. This is largely due to lack of homogenous access to quality services and corneal donor tissue, thereby impacting the waiting time for surgery and even clinical outcomes.[1,2] Effective allocation of available resources is the key to maximize outcomes from limited resources, and is critical in countries with lower and middle-income economies, such as India. Cost-effectiveness analysis in healthcare attempts at measuring the economic impact of the interventions and helps in decision-making for better allocation of resources.[3]

With evolution in surgical techniques, Descemet stripping automated endothelial keratoplasty (DSAEK) has largely replaced penetrating keratoplasty (PK) as surgical treatment of choice for patients with endothelial dysfunction.[4,5] Although it is established that DSAEK is superior to PK in terms of overall clinical outcomes, there is limited data about cost-effectiveness of DSAEK compared with PK in literature. This study aims to compare DSAEK and PK in patients with endothelial dysfunction in terms of their cost-effectiveness and cost-utility in an Indian population.

Methods

This was an ambispective observational study conducted at a tertiary care eye hospital in India over a period of 18 months. Prior approval from the institutional ethics committee was sought and the study adhered to tenets of the Declaration of Helsinki. Retrospective data collection from the hospital records revealed the list of patients who underwent DSAEK or PK for endothelial disease from January 2012 to February 2015 at the hospital. All of them were serially contacted and those fulfilling the selection criteria were enrolled in the study after obtaining a written informed consent.

Selection criteria: All patients where surgery was performed for either Fuchs endothelial corneal dystrophy (FECD), pseudophakic or aphakic bullous keratopathy (PBK, ABK) and

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congenital hereditary endothelial dystrophy (CHED) with at least 1 year of follow-up after keratoplasty were included in the study. Patients with the presence of other sight-threatening ocular comorbidities such as diabetic retinopathy, macular degeneration, advanced glaucoma, and optic atrophy and those who were not on regular follow-up were excluded.

Sample size calculation: Due to lack of similar studies in Indian population, a retrospective cohort study by Bose *et al.* analyzing the cost-effectiveness of DSEK and PK in a tertiary care hospital in Singapore was chosen as the reference.[6] Using the outcome measure as difference in effectiveness i.e., mean postoperative visual acuity, power of study as 0.8, level of significance (or α) as 0.05, and the test hypothesis that mean postoperative visual acuity of both keratoplasties is the same, the required sample size came out to be 58 in each group. Considering the average number of patients who underwent DSAEK and the limited study duration of 18 months, a minimum sample size of total 120 patients with 60 patients in each group was decided after consultation with the biostatistician.

Clinical workup and evaluation: All participants were retrospectively enrolled in the study after they had completed six months follow-up after keratoplasty. Preoperative data were obtained from hospital records. They underwent detailed interview and examination at enrollment, i.e., 6-month follow-up, and at 1-year and 2-year follow-up after surgery. The demographic details of the patient, relevant systemic history and examination findings, and details of series of events that occurred in patient's postoperative course till enrollment in the study were noted. A detailed ophthalmic examination consisting of the following parameters was conducted:

1. Visual acuity examination and refraction: unaided distance visual acuity (UDVA); best spectacle-corrected visual acuity (BSCVA) using Snellen's chart at 6 m; streak retinoscopy; subjective refraction; manifest refractive spherical equivalent (MRSE); mean refractive astigmatism. Cardiff's visual acuity was used to record visual acuity in children as applicable
2. Comprehensive external ocular, anterior segment, and posterior segment examination
3. Detailed anterior segment evaluation with particular importance to presence of any conjunctival congestion, graft status, graft clarity, status of sutures, and that of lens. Graft was considered as clear if iris details were either clearly visible or with minimal haze; else the graft was considered as failed for the purpose of this study
4. Intra-ocular pressure measurement using Goldmann's applanation tonometer
5. Examination under general anesthesia (EUA) was conducted for pediatric patients wherever deemed necessary.

Outcome Measures: Economic evaluation was done from a patient's perspective, as the burden of healthcare in our population is primarily on the patients and shared partly by government through the provision of subsidized treatment in government hospitals.[7] As the study was conducted in a government-funded tertiary care eye hospital, the estimate of cost of keratoplasty services, including eye banking, donor tissue preparation, and surgeon charges, would have largely been based on assumptions and hence was not included in the analysis.

For the comparative analysis, best-corrected visual acuity (BCVA) and corneal graft clarity were evaluated as measures of effectiveness. For the measures of cost, the total expenditure incurred by the patient was calculated over specified time points using the predefined checklist. It consisted of costs of initial surgery (cost of hospital stay plus consumables), follow-up visits, medications and optical correction, and that of short procedure for any complications (such as need for suture replacement and rebubbling). The relevant data about these expenditures were collected from hospital information system and from the patient's bills. Total cost per patient was calculated for each group at baseline, recruitment and at 1-year and 2-year follow-up visits.

Statistical analysis: The observations were recorded in an Excel sheet and statistical analysis was performed using SPSS software package (IBM SPSS Statistics for Windows, version 21.0. Armonk, New York: IBM Corp). Quantitative continuous data were compared using parametric (Student's *t* test) and nonparametric (Wilcoxon rank sum) tests based on distribution of data. Categorical variables were evaluated using the Chi-square test. The characteristics that were different between the two groups vis-à-vis baseline visual acuity, average length of follow-up, and distance traveled during each follow-up visit and statistically significant were adjusted statistically. The adjusted outcome measures viz. visual acuity and total cost at each of the three time points were derived and compared using generalized estimating equations.

An incremental cost-effectiveness ratio (ICER) was calculated (difference in cost divided by difference in effect) and interpreted using cost-effectiveness plane, which translated in this study as[7,8]:

ICER = (Cost DSAEK – Cost PK)/(Adjusted postoperative visual acuity DSAEK – Adjusted postoperative visual acuity PK)

The visual acuity (converted from Snellens to logMAR equivalent) was converted to utility using the following third-order regression polynomial derived from a log-linear plot of utility value against visual acuity in logMAR using data from Brown *et al.*[9]:

$$y = -0.479\,x + 0.191\,x - 0.4233\,x + 0.1928,$$

Where y is the utility value and x is the visual acuity in log MAR.

The incremental cost-utility ratio of DSAEK over PK was calculated as follows[10]:

ICUR = (Cost DSAEK – Cost PK)/(QALY DSAEK – QALY PK)

ICUR was interpreted as per WHO's Choosing Interventions that are Cost–Effective project (WHO-CHOICE) with cost of improving one quality-adjusted life year < per capita GDP being very cost-effective, 1–3 times GDP being cost-effective and >3 times GDP being not cost-effective.[11]

The graft survival was evaluated using Kaplan–Meier survival estimates. The difference in graft survival was tested using the log-rank test. The hazard ratio for graft failure by DSAEK was calculated.

Results

A total of 184 patients were screened from January 2012 to February 2015, of which 22 did not meet inclusion criteria, 36 failed to respond, and 6 did not consent to participation, leading to a total of 120 patients with 60 each in the PK and DSAEK group. The mean age of the patients in PK group was 48.13 ± 23 years and those in the DSAEK group

was 56.5 ± 18.5 years (P = 0.095). Pseudophakic bullous keratopathy was the most frequent indication in both PK and DSAEK groups. All patients with aphakic bullous keratopathy, who were assessed for eligibility at enrollment, had to be excluded due to the presence of advanced secondary glaucoma. Mean preoperative visual acuity was worse in PK group as compared to DSAEK group as the patients in the former group had advanced disease at presentation [Table 1].

The results obtained, broadly categorized as clinical and economic considerations, are as follows:

Clinical outcomes: Both the groups showed an improvement in visual acuity from baseline as expected. The visual acuity improvement in DSAEK group was faster than PK group [Table 2]. Difference in postoperative visual acuity between the two groups after adjusting the difference in preoperative baseline characteristics was statistically significant at 6 months [0.31 logMAR, 95% CI (0.21–0.42); $P < 0.001$] and 1 year [0.14 logMAR, 95% CI (0.07–0.20); $P < 0.001$] but not so at 2 years. Final visual acuity at 2 years was 0.32 ± 0.02 logMAR for PK group and 0.25 ± 0.02 logMAR for DSAEK group [difference 0.05 logMAR, 95%CI (0.01–0.12); P = 0.078]. It can be inferred from the data that DSAEK had better visual outcomes than PK till 1 year after surgery, following which the trend continued, though the difference in average BSCVA at 2 years was not statistically significant between the two groups.

Our patients presented late with advanced corneal disease, coupled with a long waiting period for transplantation, and hence recording preoperative spherical equivalent and astigmatism was not possible in many cases and thus, could not be used as an outcome variable. Postoperative mean refractive spherical equivalent (MRSE) after retinoscopy and subjective refraction was significantly higher in PK group at all follow-up visits. At the final follow-up median MRSE in PK group was –2D (–6D – 0.75D), whereas in the DSAEK group was 1D (–2.25D – 3D). Postoperative astigmatism was significantly higher in PK group at all follow-up visits. At 2 years median postoperative astigmatism was 1.25D (0.5D – 3D) in PK group and 0.75D (0 – 2.5D) in DSAEK group.

Total patients with an irreversible loss of graft clarity (as defined earlier as failed graft) were five in PK group and ten in DSAEK group of which five patients had primary graft failure. The time till graft failure was used to plot Kaplan-Meier survival estimates; primary graft failures were excluded from this analysis. The difference in the survival of graft was statistically insignificant between the two groups (P = 0.84) [Fig. 1]. The hazard ratio for graft failure by DSAEK was 1.13 ± 0.72 (95% CI: 0.33 to 3.9).

Comparative economic analysis: To determine the statistical difference in the cost incurred by patients in the two groups, only outcomes of patients with complete 2 years follow-up were included (N = 81). Further, as graft failure was the costliest complication, the results were analyzed separately for patients who suffered graft failure (N = 15). As baseline characteristics of the two groups were different in certain aspects, the outcomes were adjusted for confounding factors. The adjusted outcomes were determined using generalized estimating equations as described above and the cumulative cost incurred by patients of both groups are summarized in Table 3. Cost in DSAEK group was significantly higher at baseline and was adjusted for comparison at further follow-up points. At the economic front, DSAEK was significantly costlier than PK at 6 months with difference being 1273.7 INR (95%CI: 387.5 INR – 2160.1 INR; P = 0.005); however, this difference in cost was insignificant at 1 year (301.5 INR, 95% CI: -1311.9 INR – 708.9 INR; P = 0.56). At 2 years incremental cost of PK over DSAEK was statistically significant (1952.6 INR, 95%CI: 448.4 INR – 3456.8 INR; P = 0.01).

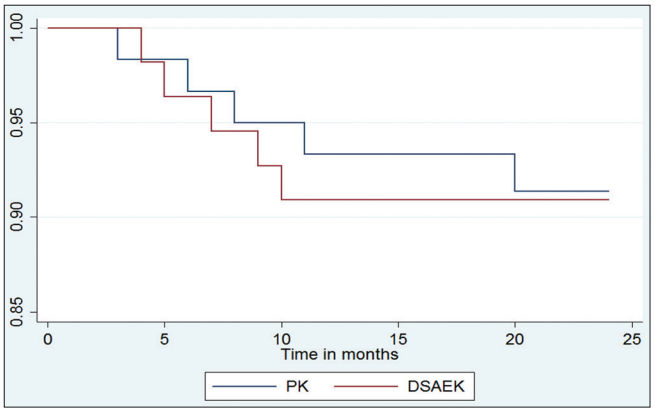

Figure 1: Kaplan–Meier Survival estimates for two groups

Table 1: Summary of baseline characteristics

Variable	PK	DSAEK	*P*
Age (years) [range]	56.5 [3-80]	61.5 [7-82]	0.09
Sex (M:F)	30:30	29:31	0.85
Diagnosis			
Pseudophakic bullous keratopathy	39	47	0.09
Fuchs endothelial dystrophy	6	7	
Congenital hereditary endothelial dystrophy	15	6	
Number of patients requiring general anesthesia (those less than 15 years of age)	6	6	1
Length of Follow-up (years)	1.87±0.34	1.68±0.47	0.017
Distance travelled per follow-up visit (km) [range]	201 [8-2650]	61 [6-2610]	0.04
Preservation media used (MK followed by Cornisol : MK alone)	24:36	21:39	0.57
Preservation to surgery interval (Days) [range]	3 [1-5]	2 [1-4]	0.28
Preoperative visual acuity (logMAR)	2.01±0.08	1.78±0.08	0.003
Preoperative utility	0.38±0.18	0.47±0.13	0.05

Table 2: Summary of clinical outcomes

Parameter	Time point	PK	DSAEK	*P*
Best spectacle corrected visual acuity (BSCVA) (logMAR), *n*=60	Baseline	2.01±0.08	1.78±0.08	0.003
	6 months	0.68±0.04	0.35±0.04	0.000
	1 year	0.40±0.02	0.25±0.02	0.000
	2 year	0.32±0.02	0.25±0.02	0.009
Median refractive spherical equivalent (MRSE) (D)	6 months	-3 [-7.5, 1.25] *n*=58	0.75 [-2.25, 3.5] *n*=53	<0.001
	1 year	-2.25 [-6, 0.75] *n*=56	1 [-2.25, 3] *n*=50	<0.001
	2 year	-2 [-6, 0.75] *n*=47	1 [-2.25, 3] *n*=34	<0.001
Median astigmatism (D)	6 months	2.5 [0.5, 6] *n*=58	0.75 [0, 3] *n*=53	<0.001
	1 year	1.5 [0.5, 4] *n*=56	0.75 [0, 3] *n*=50	<0.001
	2 year	1.25 [0.5, 3] *n*=47	0.75 [0, 2.5] *n*=34	<0.001

Table 3: Summary of difference in postoperative visual acuity and cumulative total cost outcomes, unadjusted and after adjustment for baseline differences

Outcome measure	Time (months)	PK (*n*=60)	DSAEK (*n*=60)	Unadjusted		Adjusted for difference in preoperative visual acuity	
				Difference (95% CI)	*P*	Difference (95% CI)	*P*
Visual acuity in log MAR	0	2.01±0.08	1.78±0.08	0.24 [0.16, 0.46]	0.036		
	6	0.68±0.04	0.35±0.04	0.33 [0.22, 0.43]	<0.001	0.31 [0.21, 0.42]	<0.001
	12	0.40±0.02	0.25±0.02	0.15 [0.09 , 0.21]	<0.001	0.14 [0.07, 0.20]	<0.001
	24	0.32±0.02	0.25±0.02	0.07 [0.01, 0.12]	0.021	0.05 [0.01, 0.12]	0.078
Cumulative total cost	0	3093.4±90.7	3778.9±222.7	685.5 [212.2, 1156.8]	0.004		
	6	5961.7±147	6769.9±259.4	808.2 [223.7, 1392.6]	0.007	1273.7 [387.5, 2160.1]	0.005
	12	10121.4±518.6	9354.3±371.7	-767.1 [-2017.6, 483.4]	0.229	-301.5 [-1311.9, 708.9]	0.56
	24	13511.1±803.3	11092.9±492.1	2418.2 [571.8, 4264.7]	0.01	1952.6 [448.4, 3456.8]	0.01

Table 4: Summary of cost-utility analysis

	PK		DSAEK		Incremental cost-utility ratio (ICUR)
	Visual acuity	Utility	Visual acuity	Utility	
Baseline	2.01	0.44	1.78	0.49	-1,95,260
2 years	0.32	0.79	0.25	0.8	

ICER of DSAEK relative to PK was –39,052 INR for improvement in visual acuity of 1 log MAR unit. Incremental cost-utility analysis (ICUR) of DSAEK relative to PK was –1,95,260 INR for improvement by 1 QALY [Table 4]. Per-capita GDP of India for the year 2016–2017 was 1,18,263 INR. As cost of improving one QALY with DSAEK is 1,95,260 DSAEK becomes a cost-effective procedure at willingness to pay threshold of twice the per-capita GDP.

Discussion

There is an interplay of several factors in clinical decision-making regarding choice or type of surgery for individual patients. Clinical diagnosis, anatomical involvement type of pathology apart from clinical parameter, surgical expertise, personal choice of surgeon and patient preference play a role in influencing this process. The impact of economic implications is also recognized as an additional parameter that needs to be accounted for and studied with a view to objectivizing the socioeconomic perceived concerns. This aspect needs to be taken into consideration in clinical and social context and this study has provided reliable data in real-life situation to offer some useful reference material in the Indian context.

This study was conducted in a tertiary care eye hospital catering to a large number of patients belonging to both rural and urban India.

The age, gender distribution, and the preoperative indication for in our study is similar to the previously reported literature.[6,12] The mean preoperative visual acuity in the PK group was 2.01 ± 0.08 which was higher than that in the DSAEK group which was 1.78 ± 0.08, signifying advanced disease in the patient undergoing PK. A similar trend was noted in the Singapore study as well; however, the visual acuities in the PK and DSAEK groups were similar in a Netherlands-based and USA-based study.[12,13] This reflects that patients in our population present late with the advanced corneal disease along with a long waiting period for transplantation.

The data reported in other studies were adopted from either preexisting RCT or cohort study or review of existing literature; however, the lack of a similar large population-based study in

our country was the primary reason behind performing this study with prospective data measurement in real-world setting. Similar to the Netherlands study, we evaluated the effectiveness of keratoplasty using visual acuity, spherical equivalent, and astigmatism. However, due to majority of our patients presenting late with advanced corneal disease, coupled with a long waiting period for transplantation, recording preoperative spherical equivalent and astigmatism was not possible in many cases and hence, could not be used as an outcome variable.

Five patients in PK group suffered graft failure, the cause being graft infection in one and graft rejection in rest. Of the ten patients who suffered graft failure in DSAEK group, five patients had primary graft failure. All of these patients suffered graft dislocation and were operated during the learning curve of the surgeon. The cause of failure in DSAEK group was infection in two cases and rejection in three cases. Overall, the 2-year Kaplan–Meier survival rates in both groups were statistically same as per log-rank test. After statistically adjusting for the differences in baseline characteristics, the difference in visual acuity at 6 months and 1 year was found to be statistically significant with DSAEK performing better; however, there was no difference in visual acuity at 2 years in both the groups.

The perspective of evaluation of this study was of the patient, and not that of the hospital, healthcare system or third-party payer perspective, as commonly recorded in previous studies. Therefore, the cost of medications, follow-up, optical correction, and complications were considered for the purpose of analysis. Further, as the cost of treatment is subsidized by Government at our hospital, cost of initial surgery included only the cost of consumables and that of the hospital stay, which were included in the analysis. It is safe to say that the cost of initial surgery and complications is underrepresented in our study and that the cost captured is much less than the actual cost. However, as this is common to both the groups, the incremental cost would not be affected to a large extent.

DSAEK was significantly costlier than PK at baseline and 6 months; however, a reversal of trends was noted at 1 year, with PK being costlier than DSAEK, although it did not meet the criteria for statistical significance. PK continued to remain costly than DSAEK at 2 years and the incremental cost of PK over DSAEK was statistically significant at 2 years. The higher cost of DSAEK relative to PK in the earlier part of follow-up may have been due to the increased cost of consumables, such as a keratome blade in the former, and more common use of bandage contact lens. However, as the follow-up for PK cases is often more frequent and longer than those of DSAEK, with the additional cost of longer duration of postoperative medications, it is possible that overall PK was costlier than DSAEK. As the interpretation of ICER at short time points can be fallacious, the same was calculated at 2 years. The ICER of DSAEK relative to PK was -39052 INR, implying that DSAEK can save 39,052 INR per 1 logMAR gain in visual acuity making DSAEK a dominant choice over PK. However, this is true only from patient's perspective. The results of cost-utility analysis suggest that ICUR of DSAEK relative to PK is -1,95,260 INR per QALY gained.

Both the procedures met the WHO threshold for very cost-effective interventions and hence are cost-effective as compared to no intervention.[11] DSAEK is the cost-effective procedure over PK in our population from patient's perspective in a tertiary care government hospital at 2 years. Our study is the first of its kind in our population. The postoperative costs associated with both procedures are captured well. Further studies in our population in different hospital settings with varying perspectives and varying time period may be valuable.

Conclusion

One of the major implications of the study is that as it has clearly shown in the patient population studied DSAEK has clear advantage over PK in terms of final visual acuity and cost-effectiveness analysis therefore every effort should be made to promote and facilitate endothelial transplants rather than PK in patients with endothelial dysfunction.

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Conflicts of interest

There are no conflicts of interest.

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