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Corneal transplant failure associated with smoking

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Abstract

This retrospective study was conducted in the University of Missouri's cornea transplant service from January 1, 2010 to September 30, 2015 to determine whether smoking increases the risk of corneal transplant failure. Cornea transplant patient's records were identified via the Informatics for Integrity Biology and the Bedside data query portal using the ICD-9 codes for penetrating keratoplasty (11.64), endothelial keratoplasty (11.62, 11.63 and 11.69) and 996.51 for corneal transplant failures. A total of 257 patients were identified. The study sample was 52% female and 48% male. A total of 151 patients had penetrating keratoplasty, while 106 had endothelial keratoplasty. Penetrating keratoplasty patients with a history of smoking had a significantly higher rate of transplant failure (73%) versus those with no history of smoking (53%). Endothelial keratoplasty patients with a smoking history had a slightly higher rate of transplant failure (33.3%) versus those with no history of smoking (30%). Glaucoma patients with smoking habits also had a higher transplant failure rate (70%) compared to glaucoma patients without a smoking history (52%). Further, the study showed that female smokers and younger smokers (<54) have higher transplant failure rates. Overall the study found that patients with a history of smoking have higher rates of corneal transplant failure than non-smokers.

Introduction

The cornea is an avascular, transparent tissue which serves as a primary window for the entire visual system. The health of the cornea can become compromised and may be unable to transmit light due to corneal diseases including Fuchs' corneal dystrophy [1], bullous keratopathy [2], corneal opacity [3], viral keratitis, and scarring from traumatic corneal injury [4,5]. Corneal opacity can occur at any age and most of the age-related corneal opacities begin as early as the fifth decade of life [6,7]. Corneal opacity is the fourth leading cause of blindness, next to cataract, glaucoma and age-related macular degeneration [8]. The Eye Bank Association of America reports that 10 million persons worldwide are blind due to corneal disorders [9].

Corneal transplantation is an effective method for visual restoration when the cornea becomes cloudy and can no longer transmit light to the retina. Corneal transplantation is the most successful type of tissue transplantation with an average of 40,000 corneal transplants being performed annually in the United States. Penetrating keratoplasty (PKP) is a full-thickness transplant procedure where all 5 layers are replaced with a donor cornea. PKP is a good option for visual restoration, however postoperative recovery time is relatively slow and there is frequently refractive error due to unpredictable astigmatism. The prolonged use of steroids following PKP also has associated side effects. The average success rate of PKP is about 50% at 10 years post-transplantation. Although PKP was once the most prominent type of corneal transplant, advances in surgical procedures has led to the use of partial thickness corneal transplants such as lamellar keratoplasty (LK) and endothelial keratoplasty (EK) including deep anterior lamellar keratoplasty (DALK), Descemet's stripping endothelial keratoplasty (DSEK), and Descemet's membrane endothelial keratoplasty (DMEK). In recent years, DMEK and DSEK have become a popular procedure in this field as they frequently produce a better visual outcome.

Many studies have reported factors that can decrease the success rate of corneal transplants. These include: recurrence of dystrophy, perforation, infection, scarring, corneal vascularization, glaucoma, glaucoma medications, and immune-mediated failure. However, there is a lack of information regarding the effect of smoking on corneal transplants. Case control studies have shown mixed information on the effects of smoking in organ transplants, however epidemiological studies have shown that smoking is a serious health issue that is associated with late allograft failure [10]. Cigarette smoke has been linked to various ocular diseases including macular degeneration, cataract, and optic nerve damage [11,12]. As very little is known about the effect of smoking on corneal transplants, we undertook this study to measure the outcome of PKPs and EKs among smokers and non-smokers by analyzing electronic health records (EHR) from the University of Missouri healthcare system using the Informatics for Integrating Biology and the Bedside (i2b2) database.

Materials and methods

MU health care is one of the largest health networks in the mid-Missouri region and generates a large amount of digitized clinical data that can be accessed via the i2b2 data portal. The Cerner EHR system, PathNet system, and PharmNet system provide coded data that can be extracted using International Classification of Diseases (ICD) codes. We extracted data from January 1, 2010 up until September 30, 2015, at which time the hospital adopted ICD-10 codes.

Data collection, inclusion, and exclusion criteria were followed according to the method illustrated in Figure 1. Corneal transplant patient records were identified using ICD-9 codes for PKP (11.64), EK (11.62, 11.63 and 11.69), and corneal transplant failure (996.51). Smoking status and other variables were identified using respective key words. Individuals undergoing corneal transplants were characterized with respect to age, gender, race, and other variables. The de-identified

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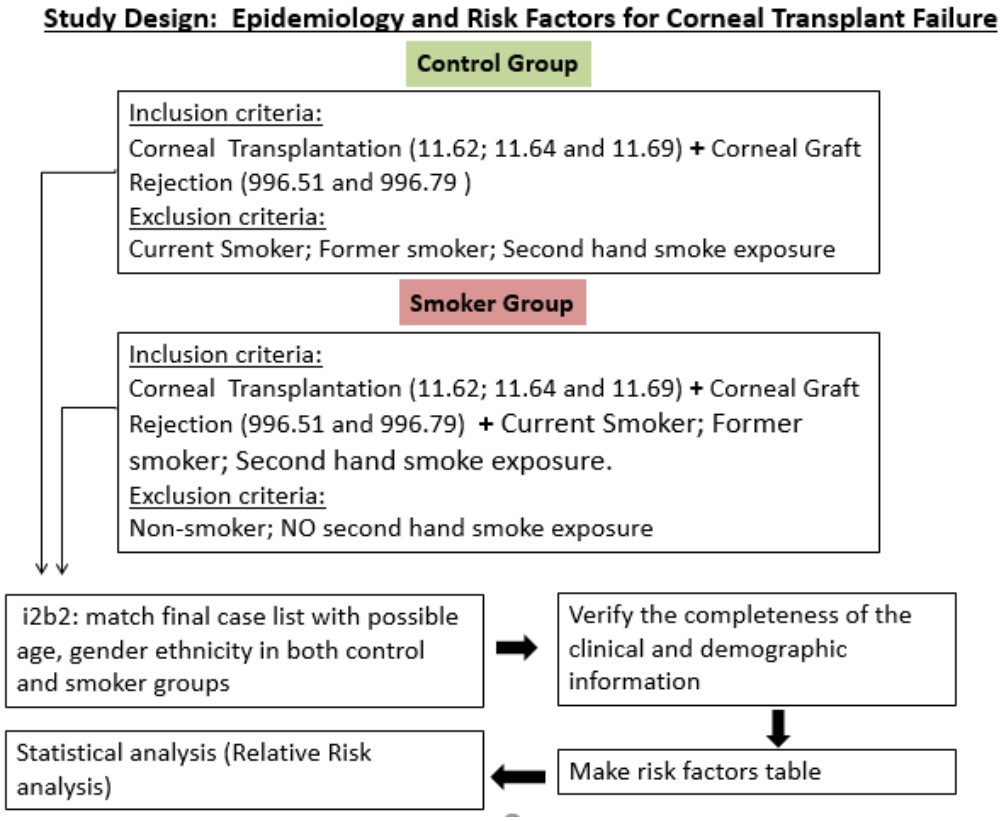

Figure 1. Study Design Flow Chart

dataset, with demographic details and time stamp of clinical events, was exported to an excel work sheet. The University of Missouri Institutional Review Board approved the study protocol.

Two hundred and fifty-seven corneal transplant records were obtained, which included 151 PKPs and 106 EKs. If a patient had both PKP and EK, then they were counted independently in each group. All smoking statuses were included as it varies with time (former smoker, current smoker, heavy smoker, and light smoker). Smoking status of the corneal donors was not obtained. Other factors including glaucoma status, hypertension, and demographic information were also included for analysis.

The association between corneal transplant failure and smoking status was assessed by univariate analysis. Relative risk (RR) and 95% confidence interval (CI) were calculated according to the method described by Daly [13]. Statistical significance was chosen as $p<0.05$ between smoker group vs non-smoker group. The RR was calculated between PKP and EK with and without smoking status.

Results

A total of 257 cornea transplant patients were identified. One hundred and fifty-one (58.7%) patients had PKP and 106 (41.3%) had EK (DMEK and DSEK). There were slightly more female (133) than male patients (124). Over 80% of the patients were 55 years or older at the time of the corneal transplant. Race was documented in approximately half of the medical records (56.8%) and distribution of race among all cornea transplant patients was as follows: 51% Caucasian, 43% unknown/other, 5% African American, >1% Asian, >1% Hispanic. The higher proportion of Caucasian patients is reflective of the mid-Missouri population. Demographic data and clinical events of all 257 cases are reported in Table 1.

Corneal transplant failure among PKP patients with a history of smoking was 73% versus 46.3% in patients with no history of smoking ($p< 0.001$; 95% CI 1.2006 to 2.0745). There was no difference in the rate of corneal transplant failure between male and female non-smokers, however there was a significantly higher rate of corneal transplant failure in female smokers (92.8%) versus male smokers (62.9%) ($p < 0.001$). There was no significant difference between the races with or without a history of smoking. The younger age groups (>55 years old) with a history of smoking had a higher rate of corneal transplant failure than the older age groups ($p<0.005$; 95% CI 1.2986 to 4.575). Detailed analysis of the PKP data can be found in Table 2. In PKP patients with glaucoma, smokers had a higher rate of corneal transplant failure (70%) than non-smokers (52.3%) (Table 3).

There was no signifcant difference in the rate of corneal transplant failure among smoking and non-smoking patients who had undergone EK (Table 4). Further analysis with a larger number of EK patients is required to validate this finding.

Overall, patients who had PKP had a higher rate of corneal transplant failure than those who had EK. Similarly, patients with a history of smoking had a higher rate of corneal transplant failure with PKP versus EK (Figure 2).

Discussion

Many risk factors have been linked with poor survival rate of corneal transplants including diabetes, glaucoma, glaucoma surgeries, and its related medication. However, no studies have addressed the effect of smoking on corneal transplantion. There is no consistent result in the literature regarding the effect of smoking on other organ transplants. The epidemiology of corneal transplant failure is complex, diverse,

Table 1. Demographic and Clinical Data of all Cornea Transplant Patients

	Description	Total	Corneal Transplant Complication	%
Corneal transplant		257	113	43.97
	Penetrating keratoplasty (11.64)	151	61	40.40
	Other corneal transplant (11.63, 11.69)	106	52	49.06
Glaucoma	No	216	69	31.94
	Yes	41	25	**60.98**
Glaucoma surgery	No	240	84	35.00
	Yes	17	10	58.82
Glaucoma medication	No	161	56	34.78
	Yes	96	38	39.58
Smoker	No	195	76	38.97
	Yes	62	37	**59.68**
Hypertension	No	135	46	34.07
	Yes	122	48	39.34
Corneal diagnostic	Bullous keratopathy (371.23)	44	20	45.45
	Corneal anesthesia and hypoesthesia (371.81)	1	0	0.00
	Keratoconus (166)	25	11	44.00
	Endothelial corneal dystrophy (371.57)	83	35	42.17
	Corneal edema due to wearing of contact lenses (371.24)	1	0	0.00
	Other posterior corneal dystrophies (371.58)	1	1	100.00
Gender	Male	124	52	41.94
	Female	133	61	45.86
Age	0-17	4	2	50.00
	18-54	47	24	51.06
	55-74	107	41	38.32
	>75	99	46	46.46
Race	African American	13	9	**69.23**
	White	130	67	51.54
	Asian	2	1	50.00
	Hispanic	1	1	100.00
	Others /UK	111	35	31.53

Table 2. PKP and Corneal Transplant Failure Among Smokers and Non-Smokers

		Penetrating Keratoplasty (PKP)									Transplant Failure Smoker vs Non-Smoker		
		Total No. of PKPs	Total Transplant Failure		Smokers	Smoker + Transplant Failure		Non-Smokers	Non-Smokers + Transplant Failure		Relative Risk	95% CI	P value
			N	%		N	%		N	%			
	PKPs	151	81	53.6	41	30	73.1	110	51	46.3	1.5782	1.2006 to 2.0745	**0.0011**
Gender	**Male**	81	38	46.9	27	17	62.9	54	21	38.8	1.6190	1.0405 to 2.5193	0.0327
	Female	70	43	61.4	14	13	92.8	56	30	53.5	1.7333	1.3050 to 2.3022	**0.0001**
Race	**Black**	12	8	66.6	6	5	83.3	6	3	50.0	1.6667	0.6937 to 4.0043	0.2534
	White	69	46	66.6	33	24	72.7	36	22	61.1	1.1901	0.8522 to 1.6620	0.3072
	Asian	1	0	0	0	0	0	1	0	0	-	-	-
	Hispanic	1	1	100	1	1	100	0	0	0	-	-	-
	Other/UK	68	26	38.2	NA	NA	NA	NA	NA	NA	NA	NA	NA
Age	**0-17**	4	2	50.0	0	0	0	2	2	100	-	-	-
	18-54	46	23	50.0	20	15	75.0	26	8	30.7	2.4375	1.2986 to 4.5751	**0.0055**
	55-74	61	32	52.4	13	9	69.2	48	23	47.9	1.4448	0.9055 to 2.3054	0.1227
	>75	40	24	60.0	8	6	75.0	32	18	56.2	1.3333	0.8059 to 2.2058	0.2627

Table 3. Glaucoma and Cornea Transplant Failure Among Smokers and Non-Smokers

Total PKPs	Glaucoma	Glaucoma + Smoker	Glaucoma + Smoker + Failure		Glaucoma + Non-Smoker	Glaucoma + Non-Smoker + Failure	
N	N	N	N	%	N	N	%
151	41	20	14	70	21	11	52.3

Table 4. EK and Corneal Transplant Failure Among Smokers and Non-Smokers

		Endothelial Keratoplasty (EK, DMEK and DSEK)									Graft Failure Smoker vs Non-Smoker		
		Total No. of EKs	Total Transplant Failure		Smokers	Smoker + Transplant Failure		Non-Smokers	Non-Smokers + Transplant Failure		Relative Risk	95% CI	P value
			N	%		N	%		N	%			
	EKs	106	32	30.1	21	7	33.3	85	25	29.4	1.133	0.5692 to 2.2567	0.7217
Gender	**Male**	43	14	32.5	9	4	44.4	34	10	29.4	1.511	0.6162 to 3.7058	0.3670
	Female	63	18	28.5	12	3	25.0	51	15	29.4	0.850	0.2921 to 2.4738	0.7656
Race	**Black**	1	1	100	0	0	0	1	1	100	-	-	-
	White	61	21	34.4	20	6	30.0	41	15	36.5	0.820	0.3754 to 1.7913	0.6186
	Asian	1	1	100	1	1	100	0	0	0	-	-	-
	Hispanic	0	0	0	0	0	0	0	0	0	-	-	-
	Other/UK	43	9	20.9	NA	NA	NA	NA	NA	NA	NA	NA	NA
Age	**0-17**	0	0	0	0	0	0	0	0	0	-	-	-
	18-54	1	1	100	0	0	0	1	1	100	-	-	-
	55-74	46	9	19.5	11	3	27.2	35	6	17.1	1.590	0.4749 to 5.3300	0.4516
	>75	59	22	37.2	10	4	40.0	49	18	36.7	1.088	0.4685 to 2.5308	0.8431

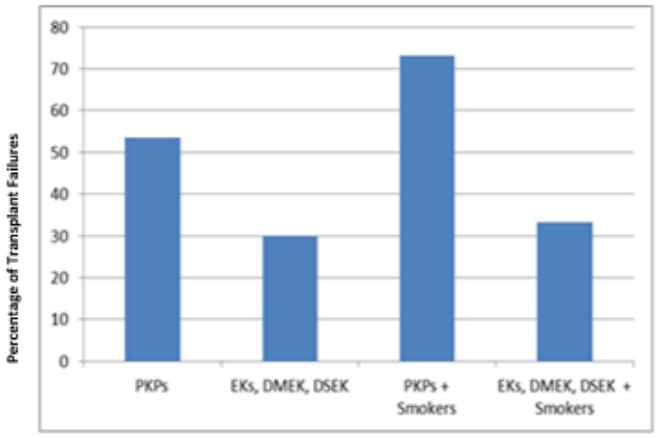

Figure 2. Comparison of Corneal Transplant Failure Among PKP and EK Patients

and varies from individual to individual. Many factors determine the survival rate of corneal transplant, including genetic variation and exposures of various endogenous and exogenous factors [14-16]. Although many clinicians perform corneal transplants, few have undertaken studies to investigate their outcome. Short-term, follow-up studies (up to 2 years) have reported success rates of up to 90% or higher in specific regions, while a few long-term studies have reported survival rates above 50% at 10 years [17]. The Australian Corneal Graft Registry shows a 10-year survival rate of 50% to 70% [18]. Similar observations were reported by the National Eye Institute Collaborative Corneal Transplantation Study [19], the United Kingdom and the Republic of Ireland Corneal Transplant Follow-up Study [20], and the Canadian Corneal Graft Outcome Study [21]. In 2008, the Australian Corneal Graft Registry reported a 10-year corneal transplant survival rate of 40% when the transplant was performed for pseudophakic and aphakic corneal edema, 60% for herpetic corneal scars, 73% for Fuchs' corneal dystrophy, and 89% for keratoconus [18]. This present study from MU healthcare data reports a 60% overall cumulative survival rate (0-6 years) with the rate of corneal transplant failures of 53% and 30% in PKPs and EKs respectively.

The burning of cigarettes releases as many 6,000 different compounds including nicotine, tobacco glycoprotein, and many toxic chemicals such as hydrocarbons, carbon monoxide, aldehydes, and heavy metals [22]. These toxic agents can cause irreversible damage to proteins and cellular systems and several studies have reported that smoking is the leading cause of ocular surface damage [23-26]. The outer layer of the cornea provides a defense mechanism and barrier to the external environment. Smoking can directly affect corneal epithelial tissue by both passive and active inhalations of smoke. The innermost endothelial layer of the cornea is a thin, monolayer of cuboidal cells covering the posterior side of Descemet's membrane which plays a key role in regulating the hydration level of the cornea through an active ATP and bicarbonate-dependent pump. Studies have reported that cigarette smoke affects endothelial cell count, guttata development, and morphological changes [27-29]. Corneal endothelial cells are sensitive to hypoxia and cigarette smoke-related hypoxia may put the endothelial cells at risk leading to corneal transplant failure.

Smoking affects both innate and adaptive immunity including inflammation and autoimmunity in many disease conditions [30]. Cigarette smoke has been shown to increase many pro-inflammatory cytokines such as IL-1, 6, 8, and TNF-α and decreased the anti-inflammatory molecule IL-10 [30,31]. Vittecoq et al reported that patients with a history of smoking and who carry at least one copy of the HLA DRB1 are at an increased risk for inflammatory disease [32]. Further case control studies with genomic and proteomics analysis could lead to the identification of potential markers in patients with a smoking history to predict corneal transplant failure.

The i2b2 database has many advantages, however it comes with limitations including an inability to comprehensively query beyond diagnosis and procedural coding. It is also limited by the data that the hospital provides. These limitations are typical of a retrospective analysis.

Overall, this study indicates that cigarette smoke plays a role in cornea transplant failure. Future studies will examine what happens at the molecular level to corneal transplants that fail in patients who smoke.

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