Factors associated with corneal transplant failure

Factores asociados a falla en el trasplante de córnea

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Abstract

Purpose: To analyze the clinical factors associated with corneal rejection before and after surgery. **Method:** In a descriptive, cross-sectional, and analytical study of 130 corneal transplants, clinical factors were studied before and after surgery. Patients of both sexes and any ages were included, with a minimum follow-up of 8 months, and tectonic procedures were excluded. A descriptive and inferential analysis was conducted for the variables of gender, previous diagnoses, vascularization, trepan size, comorbidities, and past medical history. *P* values <.05 were considered significant. **Results:** A 31% rejection rate was found. A higher risk of rejection was seen in women, previous corneal transplant or neovascularization in the recipient's cornea, and patients with glaucoma. **Conclusion:** It is necessary to plan new prospective and follow-up studies to assess accurately, and in a standard way, the clinical evolution of patients who receive a corneal transplant.

Keywords: Corneal transplant. Penetrating keratoplasty. Risk factors. Rejection.

Resumen

Objetivo: Analizar los factores clínicos antes y después de la cirugía asociados al rechazo de córnea. **Método:** Estudio descriptivo, transversal y analítico de 130 trasplantes de córnea en los que se estudiaron factores clínicos antes y después de la cirugía. Se incluyeron enfermos de ambos sexos y cualquier edad, con un seguimiento mínimo de 8 meses, excluyéndose procedimientos tectónicos. Se realizó un análisis descriptivo e inferencial para las variables sexo, diagnósticos previos, vascularización, tamaño de trépano, comorbilidad y antecedentes clínicos. Se consideró como significativo un valor de $p < 0.05$. **Resultados:** Se encontró un 31% de rechazo. Se observó un mayor riesgo de rechazo en mujeres, en caso de trasplante de córnea previo, neovascularización en córnea receptora y enfermos con glaucoma. **Conclusiones:** Es necesario proyectar nuevos estudios prospectivos y de seguimiento que permitan evaluar de forma certera y estandarizada la evolución clínica de los pacientes que reciben un trasplante de córnea.

Palabras clave: Trasplante de córnea. Queratoplastia penetrante. Factores de riesgo. Rechazo.

Introduction

Corneal transplant is a surgical procedure that has been performed for over 100 years across the world¹.

It is performed very frequently and with an excellent success rate compared to other types of organ transplants. Despite the immunological privilege^{2,3} and the lack of corneal vascularity, rejection continues to be the

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leading cause of failure in cases where surgical success is not possible⁴⁻⁸.

It is estimated that over 60 000 corneal transplants are performed each year^{9,10}. More than 30% of the patients will experience a rejection episode, and between 5% and 7% will end up in graft failure^{2,10,11}. The rejection rate reported in several studies goes from 2% to 68%².

Several different studies have identified risk factors associated with the donor and the recipient, and even intraoperative factors that have an impact on the occurrence of corneal rejection; therefore, its evaluation is crucial prior to keratoplasty. CD4+ T cell-mediated responses have been studied extensively, as well as inflammatory processes, and surgical trauma as factors that induce vascular growth within the cornea^{2,12}. Rejection rarely occurs within the first 2 weeks after the transplant, but it can occur up to 20 years later¹³.

Immunological disorders and endothelial cellular failure have been described among the primary causes. These are often associated with the donor and with the presence of primary endothelial disease, advanced age, traumatic death, use of inadequate techniques to obtain the graft or prolonged preservation time^{4,14}. Late endothelial failure is known to be the leading non-immunological secondary cause¹⁵.

In Mexico, the first reports on corneal transplants appeared back in the 1950s². The surgical factors identified in the prognosis of corneal grafts are graft size, location, and surgeries associated with the same surgical act (cataract, iris, vitreous or retina)^{9,16}. Current statistical data indicate that corneal graft survival at the 10-year follow-up is between 65% and 95%.⁵ However, this number can be smaller if the patient has another type of eye disease or disorder (stromal-endothelial dystrophy 55%, corneal leucoma 49%, trauma 33%, chemical injuries 14%)^{5,6,17}. The presence of cataracts, refraction errors, and retinal dysfunction are included among the graft-failure associated comorbidities⁹.

The objective of this study was to analyze the risk factors associated significantly with corneal transplant rejection in a reference center of Northwest Mexico.

Method

A descriptive, cross-sectional, and analytical that studied 130 individuals treated with corneal transplant at the *Centro Médico Nacional del Noroeste del Instituto Mexicano del Seguro Social*, in the city of Obregon, Sonora. The study variables included sex, age, graft vascularity, size of trepan used, comorbidity,

history of glaucoma, previous intraocular surgery, visual acuity, rejection time, combined surgery, previous corneal transplant, and preoperative diagnosis. All participants were followed for, at least, 8 months after surgery. The cases treated with penetrating keratoplasty were excluded, as well as those that did not have a preoperative diagnosis or were not followed up after the transplant. The research project was approved by the local research committee (R-2020-2602-013). All information was collected from the clinical records available at the hospital transplant coordination unit from January 2017 through December 2018. The statistical information was processed using the statistical software package SPSS, version 21.0 for Windows. For the statistical analysis a descriptive evaluation of the data was conducted with measurements of central tendency and dispersion. The inferential analysis of risk factors was conducted using contingency tables through the Pearson chi-square test by estimating the 95% confidence intervals (95%CI). A risk analysis was performed using the odds ratio (OR) to assess the factors involved in graft failure. The numerical and ratio variables were studied using Student's t-test. *P* values ≤ 0.05 were considered statistically significant.

Results

A study was conducted with 130 patients treated with penetrating keratoplasty surgery whose ages went from 15 to 88 years, with a mean age of 56 ± 19 years. Forty cases (31%; 95%CI, 23-38) showed corneal rejection. Rejection occurred more frequently in women (21 cases, 16%). The mean time until rejection occurred was 8 months. Out of the 40 cases that showed rejection, 33% occurred within the third trimester and 13% of them 12 months after the surgical procedure.

The most common preoperative diagnosis was bullous keratopathy in 56 patients (43%; 95%CI, 34-51) followed by corneal leucoma in 32 patients (25%; 95%CI, 17-32), and keratoconus in 20 patients (15%; 95%CI, 9-21). The characteristics of the study population prior to the corneal transplant are shown in [table 1](#). The comparison between visual acuity before and 12 months after the surgical procedure showed improvement in 69 patients (53%; 95%CI, 44-61), worsening in 20 patients (15%; 95%CI, 9-21), and no changes in 41 patients (32%; 95%CI, 23-39). The clinical history and the comorbidities of patients who received corneal transplants are shown in [table 2](#).

Among the factors that showed an association with a higher risk of corneal transplant rejection were the female

Table 1. Characteristics of the study population prior to the corneal transplant

	n	%	95%CI	OR	P
Age					
< 40 years	31	24	16-31		
40-60 years >	27	21	14-28		
> 60 years	72	55	46-63		
Previous diagnosis					
Bullous keratopathy	56	43	34-51	1.0	0.76
Keratoconus	20	15	9-21	0.2	0.02
Leucoma	32	25	17-32	0.7	0.41
Corneal graft rejection	12	9	4-14	1.0	0.88
Fuchs' Dystrophy	6	5	1-8.2	2.8	0.0001
Corneal ulcer	4	3	4-14	0.8	0.80

95%CI, 95% confidence interval; OR, odds ratio.

Source: clinical registries from the *Centro Médico Nacional del Noroeste* ophthalmology unit, City of Obregon, Sonora, Mexico.**Table 2.** Clinical history and comorbidities of patients treated with corneal transplant

	n	%	95%CI	OR	P
Eye operated on					
Right	58	45	38-55		
Left	71	55	46-63		
Preoperative past medical history					
Corneal transplant	18	14	8-19	2.6	0.0001
Intraocular surgery	64	49	40-57	1.2	0.38
Neovascularization in the recipient's cornea	48	37	28-45	2.0	0.004
Comorbidity					
Diabetes mellitus	29	23	14-27	1.4	0.20
Arterial hypertension	55	42	34-51	1.5	0.11
Rheumatoid disease	4	3	0.1-6	0.8	0.80
Hypothyroidism	7	5	1-9	0.9	0.80
Glaucoma	32	25	17-32	2.2	0.002

95%CI, 95% confidence interval; OR, odds ratio.

Source: clinical registries from the *Centro Médico Nacional del Noroeste* ophthalmology unit, City of Obregon, Sonora, Mexico.

sex (OR, 1.8; $P = .02$), past medical history of corneal transplant (OR, 2.6; $P = .0001$), neovascularization in the recipient's cornea (OR, 2.0; $p = 0.004$), neovascularization in the four quadrants (OR, 2.5; $P = .001$), and the presence of glaucoma (OR, 2.2; $P = .002$). As part of the preoperative diagnosis, it was found that the presence of keratoconus turned out to be a protective factor against corneal transplant failure (OR, 0.28; $P = .02$). Risk factors associated with corneal transplant failure are shown in [table 3](#).

Discussion

This study is the first one to analyze corneal transplant rejection in Northwestern Mexico. A rejection rate

Table 3. Risk factors associated with corneal transplant rejection

	Without rejection n = 90	With rejection n = 40	OR	P
Sex				
Female	28 (21.5%)	21 (16.2%)	1.8	0.02
Male	62 (47.7%)	19 (14.6%)		
Past medical history				
Corneal transplant	6 (4.6%)	12 (9.2%)	2.6	0.0001
Intraocular surgery	42 (32.3%)	22 (16.9%)	1.2	0.380
Neovascularization in the recipient's cornea	26 (20.0%)	22 (16.9%)	2.0	0.004
Comorbidity				
Diabetes mellitus	17 (12.3%)	12 (8.5%)	1.4	0.207
Arterial hypertension	34 (26.2%)	21 (16.2%)	1.5	0.117
Rheumatic disease	3 (2.3%)	1 (0.8%)	0.8	0.8
Hypothyroidism	5 (3.8%)	2 (1.5%)	0.9	0.8
Glaucoma	15 (11.5%)	17 (13.1%)	2.2	0.002
Combined surgery	13 (10%)	7 (5.4%)	1.1	0.65
Trepan size				
< 7	2 (1.5%)	1 (0.8%)	1.0	0.92
7.25-7.5	67 (51.5%)	27 (20.8%)	0.7	0.41
7.75-8.0	21 (16.2%)	12 (9.2%)	1.2	0.42

OR, odds ratio.

Source: clinical registries from the *Centro Médico Nacional del Noroeste* ophthalmology unit, City of Obregon, Sonora, Mexico.

of 31% was found, which is consistent with what has been reported by similar studies. In 110 transplant cases, Sánchez-Cornejo, et al.¹³ found a rejection rate of 52% whereas in more recent studies like the one conducted by Verdiguél Sotelo, et al.² with a cohort of 539 patients, the rejection rate was 12%. Also, Gittins-Núñez, et al.¹⁸ found a 35% rejection rate in 150 patients. In all these studies, a very wide rejection variation can be seen, perhaps due to their internal consistency and the size of the sample included for the analysis.

Several factors have been suggested for the occurrence of corneal rejection such as graft size, vascularization per number of quadrants before and after the transplant, type of suture, the patient's age, the presence of previous transplants or having associated conditions like glaucoma¹³. Rejection rarely occurs within the first 2 weeks, and it can occur after a penetrating keratoplasty¹⁹.

In our series, visual acuity at 12 months after the transplant improved in more than 50% of the cases, but not as much as in the series reported by Gittins-Núñez, et al.¹⁸ who found improvement of up to 81%. Among the factors that influenced the success of visual acuity in our study we found the presence of glaucoma with

optic nerve damage, preexisting diabetic retinopathy, and vitreous hemorrhage, among others. Studying this history should always be recommended to achieve successful surgeries.

The most common cause for performing a corneal transplant was bullous keratopathy followed by keratoconus, which is similar to what was reported in the series of patients from the study conducted by Gittins-Núñez, et al.¹⁸. This can, perhaps, be explained by the age of our population since most of them were > 60 years and many of them had a past medical history of cataract surgery. Regarding sex, the literature reviewed does not establish any associations between sex and the risk of rejection¹⁴.

Among the factors associated with early transplant rejection, we found that the most common ones are female sex, previous corneal transplant, the presence of neovascularization in the recipient's cornea, and neovascularization in the four quadrants, as well as the presence of glaucoma (as mentioned above). Of all these factors, corneal vascularization is very significant because it is the response to an aggressor phenomenon that modifies the characteristics of the cornea like inflammation, scarring or ischemia. In fact, the presence of vessels in the corneal periphery, in the four quadrants, increases the chances of graft rejection by a factor of 9¹³. Therefore, is necessary to standardize the preoperative measurement of neovascularization in the four quadrants and take the necessary measures to minimize the chances of rejection.

On the postoperative moment in which the corneal rejection episode occurred, the largest number of cases occurred within the third trimester (33%), which is different from the number of cases reported by other studies in which rejection occurred early within the first trimester after the surgery¹⁸.

The past medical history of rejection was the preoperative factor most associated with rejection whereas, keratoconus was described as a protective factor. Among the study limitations, we should mention the fact that it was retrospective, the dependence of the observations that were made by the criterion of the evaluator of the moment who did not allow to standardize the collection methodology of clinical information; however, during this study information collection, data with errors or inconsistencies were excluded to prevent interpretation or registration biases as much as possible.

Cataract surgery is one of the leading surgical procedures that performed across the world. The final outcome in the donation and transplant process depends

on multiple factors, from epidemiological characteristics of donor and recipient to the procedures that start with the retrieval, preparation of the procedure, and tissue preservation, which often requires going through a series of events that, should the established standards not be observed, jeopardizes the success of the surgical procedure^{19,20}. Therefore, is necessary to optimize the surgical technique, and conduct a close postoperative follow-up of the patients treated to provide timely care should complications occur.

Conclusions

The results of our study do not vary too much from what has been reported in similar national and international studies. It is necessary to plan new prospective and follow-up studies to assess accurately, and in a standard way, the clinical evolution of patients who receive corneal transplants.

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Conflicts of interest

The authors declare not having any conflict of interest with this study.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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