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Indications and outcomes of pediatric keratoplasty in a tertiary eye care center

A retrospective review

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Abstract

To evaluate indications and outcomes of pediatric keratoplasty in a tertiary eye center, and identify factors that affect visual outcomes.

We performed a retrospective review of penetrating keratoplasty in children aged 0 to 18 years between 1995 and 2011 in the Asociación para Evitar la Ceguera en México IAP, Hospital "Dr. Luis Sánchez Bulnes".

A total of 574 penetrating keratoplasties were performed during the study interval. Median follow-up was 5.0 years. Main indications included keratoconus (55.58%), postherpetic scarring (9.58%), traumatic opacities (7.49%), and bullous keratopathy (6.09%). Rejection rates at 5 years were 27% overall, and among indications, keratoconus showed the best graft survival at 60-months follow-up (85%). The percentage of patients with best corrected visual acuity (BCVA) posttransplant >20/400 at 5 years in the nonrejection group was 81.25% and 82.74% in < and > 10 years of age (YOA) groups, respectively, versus a BCVA posttransplant > 20/400 at 5 years in the rejection group of 53.68% and 51.72% in < and > 10 YOA groups, respectively. There was a statistically significant reduced rejection rate between genders at 18 months of follow-up, favoring males.

Despite being considered a high-risk procedure in children, penetrating keratoplasty can achieve good results, especially in patients with keratoconus. It can achieve significative improvements of visual acuity, provided there is an adequate follow-up and treatment adherence.

Abbreviations: BCVA = best corrected visual acuity, CHED = congenital hereditary endothelial dystrophy, DALK = deep anterior lamellar keratoplasty, HLA = human leukocyte antigens, YOA = years of age.

Keywords: cornea, corneal transplant, keratoplasty in children, pediatric corneal transplant, pediatric keratoplasty

1. Introduction

Among the most frequent ocular pathologies, there are corneal disorders secondary to trauma, chemical burns and infectious diseases, as well as congenital entities. Most of these disorders require surgical treatment, mainly with penetrating keratoplasty. These corneal alterations are prevalent in the pediatric population, which is a challenging one due to tissue characteristics—reduced ocular[1] and scleral rigidity that increase the likelihood of refractive errors after corneal transplantation,[2] severe inflammation after surgery, among other factors like rehabilitation issues due to poor patient cooperation.

Besides, there is a well-known increased incidence of graft failure in pediatric patients, reported more than 30 years ago,[3] and some studies suggest it is secondary to involvement of innate immunity,[4] the primary defense system in children. Since then, there has been a widespread notion that outcomes of pediatric keratoplasty are not as good as in adults,[5] and although success rates have improved over the years, there is controversy about the indications for keratoplasty and postsurgical treatment in this group of patients. Although some authors recognize that anatomic success of pediatric keratoplasty is increasing,[6] there are still several factors to take into consideration.

To date, several efforts have been made to improve visual and functional outcomes in children, and although keratoplasty remains the surgery of choice for the management of pediatric corneal disease incurable by medical treatment, some authors have proposed other approaches. Among these, contact lens wear in selected corneal opacities,[7] use of keratoprosthesis,[8] as well as different surgical techniques like rotational autokeratoplasty[9,10] and deep anterior lamellar keratoplasty (DALK)[11–13] have been proposed; the former restricted only for specific cases, and the latter with unclear long-term results and not suitable for all patients.[14] Regarding keratoplasty, most authors agree that smaller grafts and interrupted single sutures may improve postoperative outcome in children.[15,16] Nevertheless, these efforts have not been limited to the selection and performance of the most adequate technique.

Editor: Khaled Ahmed Abdelrahman.

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:45(e8587)

Received: 27 September 2017 / Received in final form: 17 October 2017 / Accepted: 23 October 2017

http://dx.doi.org/10.1097/MD.0000000000008587

Different options have been proposed to improve graft survival, as human leukocyte antigens (HLA) HLA-A, -B, and -DR antigen match. But results have been conflicting: some authors report there is no effect of HLA antigen matching on overall graft survival, and other authors also report that ABO blood group matching may be effective to reduce the risk of graft failure.[17,18] On the other hand, other authors state that HLA-A and HLA-B antigen match improve graft survival and reduce the risk of rejection.[19–21] Besides, to achieve better results, postoperative pharmacologic treatment as topical cyclosporine[22] and antiangiogenic therapy[23] have been advocated as useful adjunctive treatments in addition to topical corticosteroids.

Nevertheless, there are marked differences in outcomes depending on the preoperative diagnosis.[24] For example, Peters anomaly presents a high risk of graft failure: 39% at 1 year,[25] 38% at 3 years,[26] and 70% at 5 years,[27] with high consistency in graft failure rates between publications. Children with glaucoma[28] and those subjected to regrafting show poorer prognosis.[29] On the other hand, although there are country differences between the main indications for pediatric keratoplasty, like infectious keratitis in India[30,31] or mechanical trauma and infectious keratitis in North China,[32] one of the most frequent indications for keratoplasty in children worldwide is keratoconus, which shows the best outcomes within subgroups.[33] Even in children with Down syndrome and keratoconus, where we would expect less patient cooperation, 5-year graft survival rates are good.[34] Finally, congenital hereditary endothelial dystrophy (CHED), another relatively frequent indication for early keratoplasty, has been reported as an entity with a moderate postoperative visual success.[35,36]

Due to the complexity of this subject from preoperative decision making to postsurgical management, we aimed to contribute with our 17-year experience in pediatric keratoplasty in a tertiary eye center; exhaustive reviews about keratoplasty in children can be found elsewhere,[37–39] with comprehensive data about the main studies published regarding this subject.[40]

2. Materials and methods

2.1. Study design

This is a retrospective and analytic study approved by the Internal Review Board of the Asociación para Evitar la Ceguera en México I.A.P., "Hospital Dr. Luis Sánchez Bulnes", in Mexico City, Mexico. All the procedures conformed to the tenets of the Declaration of Helsinki. All participants (or their legally acceptable representatives) signed a written informed consent before the surgical procedure.

2.2. Population and measurements

We performed a retrospective review from 1995 to 2011 of the medical records of all cases of keratoplasty in patients aged ≤ 18 years. We extracted the following data for our database: patient demographics, initial BCVA, yearly BCVA during the 5-year postprocedural period, examination findings, ocular diagnoses, performed surgeries, graft clarity during 5-year follow-up, time to graft failure. Medical records with incomplete data were excluded. Main outcome measurements were BCVA at 5 years, and presence/ absence of rejection as defined in previous publications.[41]

Table 1

Indications by frequency.

Indication	Number of eyes	Percentage (%)
Keratoconus	319	55.58
Postherpetic scarring	55	9.58
Traumatic opacities	43	7.49
Bullous keratopathy	35	6.09
Bacterial/mycotic ulcers	33	5.74
Corneal opacity/leukoma NOS†	19	3.30
Miscellaneous*	70	12.15

* Miscellaneous included keratoglobus, congenital glaucoma, previous graft rejection, corneal burns, corneal dystrophies, peters anomaly, sclerocornea, Axenfeld–Rieger syndrome, staphyloma, hematic impregnation of the cornea, amyloidosis, microcornea, dermoid cyst, rosacea.
† NOS: not otherwise specified.

2.3. Statistical analysis

A paired Student *t* test was used to assess statistical significance between groups in normally distributed data, whereas the Wilcoxon matched pairs signed-rank test was employed for non-normal distributed data. In addition, the Kaplan–Meier method with the Log-rank (Mantel–Cox test) was used to assess survival rates among keratoplasty groups. Pearson correlation coefficient and linear regression analyses were used for rejection graft data as well as age. Normal and non-normal distributions were determined by Shapiro–Wilk tests for all variables. BCVA analyses used logMAR notation, but BCVA is presented as Snellen values within the text and in tables. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software (version 20, SPSS Inc, Chicago, IL). Graphs and layouts depicted in all figures included were elaborated using the 2015 GraphPad software Inc. Prism version 6.0.

3. Results

Five hundred seventy-four penetrating keratoplasties were performed during the study interval with complete medical records. Mean age was 11.91 ± 4.35 years. Mean follow-up was 5.0 years. Main indications (by frequency) included keratoconus in 319 eyes (55.58%), postherpetic scarring in 55 eyes (9.58%), traumatic opacities in 43 eyes (7.49%), and bullous keratopathy in 35 eyes (6.09%) (Table 1).

Our results indicated that there was no difference in gender distribution ($P = .119$, Fig. 1). Rejection rate at 60 months was

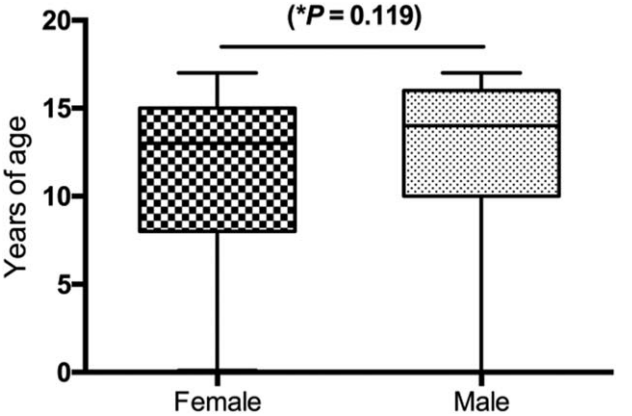

Figure 1. Gender comparison. *Unpaired *t* test ($P = .119$).

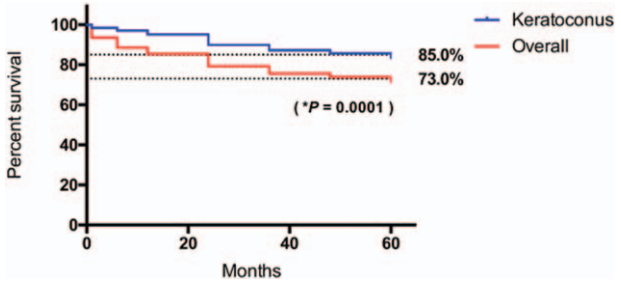

Figure 2. Graft survival in keratoconus patients compared with the overall keratoplasty population. *Log-rank (Mantel–Cox) test.

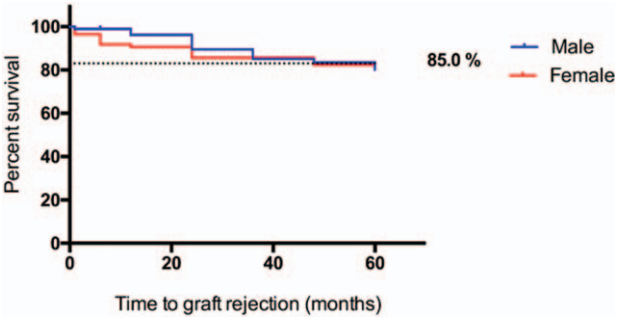

Figure 3. Survival proportions: graft survival in keratoconus: male/female. *Log-rank (Mantel–Cox) test.

27% overall, and among indications, keratoconus showed the best graft survival at 60-months follow-up (85%), with a statistically significant difference compared with the rest of indications ($P=.0001$, Fig. 2). Interestingly, we found a statistically significant difference between genders in keratoconus patients regarding graft survival in the first 3 years, favoring males (Fig. 3).

Overall, the percentage of patients with best corrected visual acuity (BCVA) posttransplant >20/400 at 5 years in the nonrejection group was 81.25% and 82.74% in < and > 10 YOA groups, respectively, versus a BCVA posttransplant > 20/400 at 5 years in the rejection group of 53.68% and 51.72% in < and > 10 YOA groups, respectively (Table 2).

Also, the mean time of graft-rejection after surgery was 20.75 ± 18.21 months. In addition, we found a statistically significant difference when comparing pre-surgical BCVA values to those obtained at 60-months follow-up for both groups of age (Table 3).

4. Discussion

Penetrating keratoplasty in children and adolescents is a challenging surgery, not only regarding the surgical procedure per se, but also during follow-up and rehabilitation. In addition, it poses a higher risk of graft rejection compared with adults, due to a stronger immunological response in young patients. The graft survival rate reported 1 and 2 years after surgery is around 80% and 67%, respectively,[42] but reports on 5-year graft survival range from 50% to 91%, depending on the series.[43–45] In our study, 2-year graft survival was 79.09%, and 5-year graft survival was 73% in the whole population of the study, which is consistent with the graft survival rates reported in other tertiary eye care centers.[30] Similarly, our graft survival rate for keratoconus was higher compared with the rest of indications ($P=.0001$, Fig. 2). Of note, graft survival rates for keratoconus patients varied between genders in the first 2 years: females

Table 2

BCVA with and without graft rejection per group of age.

	< 10 YOA*		> 10 YOA†	
	BCVA (%) w/o rejection	BCVA (%) w/ rejection	BCVA (%) w/o rejection	BCVA (%) w/ rejection
Hands motion	0	14.81	5.17	24.13
Counting fingers	4.7	22.22	6.03	20.68
20/400	14.05	9.25	6.03	3.44
20/80–20/ 200	18.75	18.51	12.06	17.24
20/60–20/40	12.50	25.92	30.17	34.48
20/30–20/20	50.00	9.25	40.51	0

BCVA values evaluated at 60-mo follow-up.
BCVA = best corrected visual acuity, w/ = with, w/o = without, YOA = years of age.
* *P* value: <.0002 for comparison between w/o and w/ rejection groups.
† *P* value: <.0001 for comparison between w/o and w/ rejection groups.

Table 3

BCVA pre- and posttransplant per group of age.

	< 10 YOA*		> 10 YOA*	
	Pretransplant BCVA (%)	Posttransplant BCVA (%)	Pretransplant BCVA (%)	Posttransplant BCVA (%)
Hands motion	42.39	14.28	12.70	6.38
Counting fingers	46.73	21.42	62.70	12.05
20/400	0	2.38	0.80	0.70
20/80–20/ 200	8.69	19.04	16.75	13.47
20/60–20/40	2.17	30.95	6.75	26.95
20/30–20/20	0	11.90	0.26	40.42

* *P* values < .05 for both age groups.
BCVA = best corrected visual acuity, YOA = years of age.

presented a higher graft rejection with a peak at 18 months after the procedure; nevertheless, at 24 months this difference was no longer observed.

To the best of our knowledge, it has not been previously reported a gender difference regarding graft survival in children; but there are some studies showing significant differences in adults. The Australian Corneal Graft Registry and The Canadian Corneal Graft Outcome study reported statistically significant gender differences in adults, showing that females were more likely to have a rejection event compared with males. However, the causes of these differences were not discussed.[46–49] Another proposed explanation is the augmented activity of the immune system in females that increases the incidence of autoimmune conditions.[50]

One possible mechanism to explain that young females present higher numbers of rejection events, may be the mismatching between the gender of the donor and the recipient. A study published in the *American Journal of Transplantation* indicated poorer outcomes in women who received corneas from males.[51] This study explains that this effect, only observed in females, is a consequence of H-Y antigen incompatibility related to the Y chromosome; the lack of Y chromosome allows compatibility from female donors to male recipients.[52] In addition, steroid hormones are involved in female graft rejection susceptibility.[53] Specifically, estrogens may be immunostimulatory by regulating lymphocyte development and function,[54] whereas some androgens are capable of inducing an immunosuppressive response by reducing lymphocyte proliferation and differentiation;[55] the latter could be the reason for the apparent protection observed in males in this study.

Nevertheless, since the effects of androgens vary considerably due to the level of exposure and diverse factors may contribute to the immune profile in females, the potential role of hormones in gender-specific immune function related to graft survival remains to be elucidated.

Regarding indications for keratoplasty, similar to other series,[56] keratoconus was the leading indication for transplant in over half of the patients (55.58%). Surprisingly, we only found 33 cases (5.74%) of infectious keratitis in children who underwent corneal transplant, which is a low number compared with other authors who report infectious keratitis as the primary indication for pediatric keratoplasty in developing countries.[30,31] This apparent low incidence of keratoplasty is due to our preferred surgical choice in these cases: conjunctival flap. The election of conjunctival flap over keratoplasty in children is due to the following reasons: higher risk of rejection, higher risk of an early second procedure that increases the risk of complications, and because children sometimes are noncompliant with treatment. In addition, conjunctival flap does not increase the risk of rejection in the long term.

Consistent with the literature, our patients with less frequent pathologies like Peters anomaly, sclerocornea, and Axenfeld–Rieger syndrome, which usually present several ocular comorbidities and undergo combined procedures, had the worst outcomes with high rejection rates. For example, despite other authors reporting good outcomes for CHED, we had 6 cases with very bad outcomes: all of them were in the graft rejection group.[57] This was also the case for congenital glaucoma, with 13 cases in our series, all of them with a poor outcome, as reported by other authors.[58] Nevertheless, other authors report similar graft survival rates irrespective of etiology.[59–61]

Age is another important factor related to the success of penetrating keratoplasty. It has been established that older children have better prognosis,[62,63] and this is consistent with our findings. As depicted in Table 2, corneal transplantation improved overall posttransplant BCVA regardless of age ($P = .002$ and $P = .0001$, respectively), but the > 10 YOA group showed better BCVA postsurgery. A significant correlation was observed between graft-rejection and age in months ($r = 0.153$; $R^2 = 0.023$; $P = .048$), with a mean age at rejection of $10.84 + 4.80$ years.

Finally, we can conclude that overall, penetrating keratoplasty is a procedure that can achieve good results in children with keratoconus,[64] provided there is an adequate follow-up and treatment, as in the case of the patients included in this study.

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