ABSTRACT

Objective: The lower recommended age of the donor cornea is a controversial matter. Although newborn corneas have a high endothelial cell density, there are anatomical, refractive (myopic shift) and postoperative problems. Two cases are analyzed; one had an atypical refractive result and the other an unexpectedly severe immune response. We also review the use of pediatric donor corneas in penetrating keratoplasty.

Methods: Two young patients with keratoconus, in whom a penetrating keratoplasty was done using a 4-month-old newborn corneal donor with high endothelial cell density (4,500 cell/mm²) are reported.

Results: In the early postoperative period, both had high hypermetropy with weak astigmatism that improved over the next few months. In one patient a marked increase in the astigmatism after removal of the continuous suture was observed. One and a half years after the penetrating keratoplasty there was V=1 corrected vision and the endothelial population was almost unchanged (4,300 cell/mm²). The other patient suffered an allograft reaction with corneal oedema in the seventh postoperative month, and subsequent rupture of the continuous suture made its early removal necessary. The oedema par...
tially diminished with high doses of steroids, but still persisted eighteen months later.

**Conclusion:** The newborn corneal graft might have led to an early strong hypermetropia as opposed to the supposed myopic shift referred to in the literature. The extremely rapid healing seen in young recipients may lead to early loosening of the continuous suture. High endothelial cell density increases the risk of irreversible graft failure probably due to a high antigenic response. The use of a newborn donor cornea is questionable due to unpredictable refractive and immunological responses (Arch Soc Esp Oftalmol 2008; 83: 219-230).

**Key words:** Penetrating keratoplasty, newborn infant, corneal graft, donor, hypermetropia.

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**INTRODUCTION**

The adequate age ranges for cornea donors is a subject of discussion among eye banks and surgeons which, for the time being, has not reached consensus (1-3).

Although the upper age limit for donors has been established around 75, the medical standards of the Eye Bank American Association (EBAA) subordinate donor and acceptance to the surgeon’s criteria and the Eye Bank chief on the basis of the potential feasibility of the corneal tissue and particularly the endothelium, dependent mainly on the cellular density which can be verified through optical or mirror microscopy (4).

In what concerns the lower age limit, most centers accept tissue from pediatric donors over 6 months of age. In this case, the criterion is not based on the endothelial population (theoretically very high in childhood and supposedly providing an improved protection of the graft vis-à-vis a possible intra- and post-op loss) but an attempt to minimize a number of problems: a) of a technical nature, linked to the transplanting of immature tissue, b) of a functional nature, derived from size differences and greater curvature of children’s cornea which can influence the visual result due to inducing a strong myopization of the graft, and finally, c) of a clinical nature, dependent on an alleged greater antigenic capacity of infant tissue which would increase the risk of immune rejection and therefore the feasibility and definitive transparency of the transplant.

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Two cases are presented, which utilized the cornea of a 4-month infant, observing in both an initial hypermetrope non-typical post-op refractive result and, in one, a disproportionate immune response. This review is based on these two cases to discuss the use of pediatric donor grafts in penetrating keratoplasty.

**SUBJECTS, MATERIAL AND METHODS**

The donor was a breast-fed infant who died of crib death. The interval between demise and enucleation was 1.5 hours. The left eye was kept refrigerated at 4°C to use it for hetero transplant of limbal cells, while in the right eye a corneal-scleral button was removed and introduced in Optisol® preservation medium. In both cases, the maintenance period was of 36 hours. The endothelial evaluation with Eye Bank mirror microscope (Konan EKA-98) was made for the left eye (OI): 4,950 cel/mm² and in the right eye (OD): 4,934 cel/mm² (fig. 1). In both, the corneal diameter was of 10 mm.

The first receptor was a 16-year old female with bilateral keratocone, more marked in the left eye, who exhibited a visual acuity with contact lenses of: LE V= 0.5 and RE V= 0.6, with low tolerance to said lenses. Her corneal topography showed in the left eye an inferior temporal ectasia, with an astigmatism of 8.26 D and in the right eye an inferior paracentral ectasia with an astigmatism of 7.0 D...
Fig. 1: 4-month old infant donor cornea. Corneal diameter 10 mm in both eyes. Endothelial microscopy: OI: 4,950 cel/mm²; OD: 4,934 cel/mm².

Endothelial microscopy showed 2,915 cel/mm² in the left eye and 2,957 cel/mm² in the right one. She was operated, under general anesthesia, for left eye penetrating keratoplasty. A trephination on the epithelial side of the complete fresh donor globe was performed with a manual 7.5 mm trephinator having the same diameter as the receiving cornea, with a Barron-Hessburg trephinator, without events to report. A continuous suture was made with single-filament nylon 10/0, with a final readjustment under surgical keratoscope (Nevyas 360°). Post-op developed normally, with a topical medication of antibiotic and corticoid being applied during one month, followed by topical corticoid in decreasing dosage for one year.

The second receptor was an 18 year-old male (contact lens user) with bilateral keratocone. The corrected visual acuity in the right eye was of V=1 and in the left eye of V=0.05. The LE showed stria-tions in the posterior face and a slight diffuse opacity in the inferior paracentral area. The corneal topography exhibited a marked central keratocone in the LE with an astigmatism of 25 D (KS: 67.89 D; KF: 42.21 D) and in the RE a slight inferior
keratocone and slight astigmatism (KS: 44.19 D; KF: 42.10 D) (fig. 3). Endothelial microscopy was of 2,971 cel/mm² in the LE. The patient was operated under general anesthesia for LE penetrating keratoplasty, detaching the donor corneal-scleral button through the endothelial side with a 7.5mm Barron punch having the same diameter (7.5 mm) in the receptor, with a Barron-Hesburg trephinator, without events. The graft was fixed with 10/0 single filament nylon continuous suture and adjusted through control with the surgical keratoscope (Nevyas 360°). The post-op course was normal. Topical antibiotic and corticoid treatment was prescribed for four weeks, followed by corticoid eye drops in decreasing dosage.

RESULTS

One month after the intervention, the first patient exhibited a transparent graft, moderate astigmatism and an intense hyperemmetrope spherical defect (+2 cil 120 + 8 sph.). With this correction, visual acuity was of V= 0.7. The topography indicated a marked flattening of the graft (KS: 39.49 D./ KF: 35.41 D.) (fig. 4). Subsequent controls showed minor modifications with transparency of the graft and persistence of moderate astigmatism and only a small reduction of hypermetropy with somewhat higher keratometric values. Eleven months later a moderate reduction of initial hypermetropy was observed (+1.75 cil 100 + 5.50 sph.), with increased

Fig. 3: Patient 2. Male, 18 years. Keratocone in both eyes. A: Left eye; B: LE endothelial microscopy; C: LE corneal topography; D: RE corneal topography.
keratometry figures (KS: 42.45 D/KF 40.27 D), with corrected visual acuity being of V= 1. Biom-etry showed an axial length of 21.54 mm (22.08 mm in the right); ocular pressure was of 10 mmHg, pachymetry of 507 µm, and endothelial microscopy showed a cell density of 4,941 cel/mm², matching the preop value of the donor cornea (fig. 5). One year after the intervention, the continuous suture was removed after which a marked increase of astigmatism was observed up to 12.12 D (KS 53.38 D/KF 41.26 D) (fig. 6). Even so, the corrected VA reached V=1 (+12 cil 60º -3.50 sph.). No corrective eyeglasses were prescribed at that time. Two months after removing the suture, arcuate keratoto-mies were made in the meridian with the largest curvature, 0.5 mm inside the interphase, 70º wide, with reinforcing points of monofilament 10/0 in the opposite meridian. This produced a marked reduc-tion of astigmatism (just under 8 D) to a value of 4.6 D (KS 47.44 D/KF 42.78 D) and, after separating the reinforcing points, showed a visual acuity with correction (+4.50 cil 65 –0.50 sph.) of V=1. Eighteen months after the transplant, the graft maintained transparency and the patient exhibited a stable astigmatism of 4.6 D with an increase of corneal curvature (KS 50.41 D / KF 45.72 D) (fig. 7) which

Fig. 4: Patient 1. Variation of corneal topography. A: after 12 months; B: after 6 months; C: after 1 year.

Fig. 5: Patient 1. One year after LE keratoplasty. A: transparent graft, stable continuous suture; B: endothelial microscopy (4,941 cel/mm²). C, D, E and F: confocal Microscopy; G: LE axial length (21.54 mm); F: RE axial length (22.08 mm).
increased the myopic component of the mixed astigmatism, significantly reducing the initial hypermetropy (+ 4.50 cil 65° –2.50 sph.), with a corrected visual acuity of V= 1. Mirror microscopy showed an endothelial density just below 4,300 cel/mm².

One month after the operation, the second patient exhibited transparent graft, stable suture, slight astigmatism, strong spherical hypermetropy and a marked corneal flattening (KS: 33.07 D; KF: 29.29 D), reaching a visual acuity of V=0.7 with correction (+3 cil. 110° + 7 sph.). Six months later, the hypermetrope defect persisted while the flattening reduced but the astigmatism increased (KS: 40.91 D; KF: 34.91 D) (fig. 8) persisting with eyeglass correction (+ 6 cil 80 + 2 sph.) the same visual acuity.

Fig. 6: Patient 1. After removal of the continuous suture 12 months after the intervention. A: transparent graft; B: marked increase of astigmatism.

Fig. 7: Patient 1. A: Arcuate keratotomy with reinforcing points; B: topography 18 months after the transplant and after astigmatism surgery.
acuity of V=0.7. Having interrupted topical corticoid treatment after 7 months, the patient visited the emergency ward referring blurred vision starting 4 days earlier in the transplanted eye, previously treated in another hospital with tobramycin and dexametason eye drops (Tobradex®, topical cyclopegic and oral Deflazocort 30 mg (Zamene®). The eye exploration revealed a marked diffuse edema due to endothelial rejection (fig. 9). An additional treatment was applied with a single IV megadose of 500 mg methylprednisolone (Urbason®) and frequent instillation (every hour) of dexametasone eye drops (Maxidex®). In successive days the intense topical treatment was maintained without observing appreciable improvements. One month later, maintaining the topical treatment against rejection, the patient returned to the emergency ward referring a foreign body feeling and mucous secretion, with edematous cornea and rupture of the continuous suture between 9 and 11 o’clock, with the distal ends of the suture buried in parenchyma and without apparent neovascularization. However, 10 days later we proceeded to separate the continuous suture, maintaining the therapy with frequent topical corticoids. In successive controls a slight improvement was evidenced even with persistence of the edema which prevented endothelial and confocal microscopy, thickened graft with a pachymetry of 902 µm (right eye 578 µm) and an ocular pressure of 20 mmHg (right eye 15 mmHg), axial length of 24.14 mm (right eye 24.53 mm). The corneal topography showed an increase of astigmatism up to 10.28 D with small curvature variations (KS: 41.08 ; KF: 30.80 D) and a visual acuity of 0.1. The topical treatment was maintained with corticoids in descending dosages. Eighteen months after the intervention the topography showed modifications with a marked increase of astigmatism (26.28 D), observing an improvement in the edema which persisted in the central portion of the graft with transparent periphery. The endothelial density cannot be assessed through mirror or confocal microscopy. For the time being, we decided to await developments before considering an additional keratoplasty.

**DISCUSSION**

From the anatomical viewpoint, the newborn cornea differs from the adult cornea in anatomical size as well as in structural and functional characteristics.

The mean corneal diameter of newborns is of about 10 mm, even smaller in premature births (5,6) and rapidly increases to reach values between 11.6 and 11.7 mm at 12 months of age (7-10), close to the 12 mm of the developed eye. The thickness (0.57 mm) is somewhat smaller than the adult cornea (0.6 mm) although Insler (11) refers similar values without finding correlation with the larger curvature. The curvature radius is of approx. 7 mm (9) and even smaller (11), which causes a greater dioptric power. There seems to be a correlation between the radius and a smaller axial length, which would compensate the hypermetropy expected in infants (9). A marked increase of corneal curvature has been seen in premature newborns (about 53-54 D) which flattens out considerably during the last months of gestation (12,13). In newborns within term, the corneal curvature is also higher than in adults, with a power of approximately 47 D (10.12-14) which goes down in the first 6 months. Even though the corneal diameter increases in the postnatal period and stops after age 2, the corneal cur-

![Fig. 8: Patient 2. corneal topography. A: at 3 months; B: at 6 months; C: at 12 months.](image-url)
curvature seems to stabilize earlier, reaching adult values in the course of the second half of the infant’s first year (10,12,13,15-17).

At the structural level, the stroma exhibits peculiar characteristics in early childhood. At birth, the cellular elements are relatively numerous, even though during the 2 or 3 first years of post-natal life the number of corneal corpuscles gradually reduces and the collagen network is poorer, with a proportional increase of fibrous elements (18). This circumstance, possibly necessary to achieve an adequate emmetropization of the eye, gives the newborn cornea a greater flexibility and elasticity in comparison with the developed eye. However, the nature of the corneal stromal matrix of the child is partially unknown (10).

It is clear that the endothelial ocular density is greater and exhibits a more regular morphology in newborns and children than in adults (19-22). Bahn (23) refers cellular density numbers in newborns of up to 6,000 cel/mm\(^2\), which are reduced considerably in the early post-natal period, particularly

Fig. 9: Patient 2. A: transparent graft at 6 months; B: endothelial rejections (8 months), in addition to the graft maintaining the suture; C: slight improvement of the edema after suture removal (10 months); D: persistence of edema after 18 months.
coinciding with the corneal diameter increase. In children between 6 days and 12 months of age, Spe-edwell (24) found a marked variability, ranging between 2,987 and 5,624 cel/mm², always in newborns under 2 months of age. In a series of children between 5 and 15 years of age, Müller and Doughty (25) obtained mean values of 3,542 (SD 510) cells/mm² (range from 2,404 to 4,817). Even though the increase of the corneal diameter reduces the endothelial density because it has to link to a larger surface (26), there is a large variability in the results of different studies about changes in endothelial cell population throughout life. Although there is a cellular reduction per area unit in the first year of life, it is not clear whether this is due to individual cell density variance at birth (24,26-28), to cell loss, to corneal growth or to a combination of all these factors (19,23,29,30). However, it seems that the diameter increase is a determining factor (21,23,31-36).

The smaller size of breastfed infant cornea, its marked flexibility, greater curvature and dioptr power, together with its high endothelial density, produce a particular tissue and immune response which can give rise to a number of problems, basically at the surgical, refraction and clinical level, as follows.

A) Surgical Problems

The smaller corneal diameter of the infant involves a limitation in the size of the donor sclero-cor-neal button and makes trephination more difficult. The trephination must necessarily be very well centered to avoid including scleral or conjunctival tissue or episcleral remains of the donor eye in the graft. It is particularly important to obtain a precise intra-stromal placement of the sutures, ideally at the pre-descemet level. Sutures which are too deep or inadvertently transfixiating may cause perforation liable to potential complications such as micro filtrations of the incision and athalamia, increasing the risk of endophthalmitis. On the contrary, excessively superficial sutures may tear the tissue, causing the loss of the effect at that level and possible high astigmatism or induce posterior dehiscence of the incision.

An excessively thin infantile cornea located over a thickened and edematous receiving bed, may cause a significant disparity in the donor-receptor thickness, causing a deficient apposition of Descemet’s membrane or both increased by its possible retraction after trephination due to the poorer collagen fabric, which may give rise to an undesirable scaling of the edge of the wound and a greater curving of the graft (10).

The excessive curvature of the infant corneal button may also cause mishaps during trephination on the endothelial side with punch. As the Teflon block has a relatively flat radius suited to the average of the adult eye, but faulty adaptation to its bed causes inadequate pressure in the centre of the graft giving rise to endothelial folds, sections with diameters above the estimates or an angled cut of the edges which can only be avoided by carrying out trephination on the epithelial face on the entire ocular globe.

B) Refractive Problems

Even though the greater flexibility of infantile cornea would in theory facilitate an earlier adaptation to a normal contour and to provide a faster visual recovery, this extreme elasticity combined with smaller thickness and greater curvature may cause excessively high residual refraction defects.

In this regard, it is considered that the most important refractive complication associated to the use of infantile cornea may possibly be the induction of post-op myopia (37,38). Vannas (39) describes a severe myopia when utilizing newborn corneas. Wood (40) observed myopic refraction and related it to a greater curvature of the anterior corneal surface. For this reason, in a stage prior to the common use of intra-ocular lenses associated to keratoplasty, it was suggested to utilize infantile corneae as a possible refractive surgery alternative for correction of unilateral aphakia (40,41) as well as in cases of penetrating keratoplasty combined simultaneously with intracapsular extraction of cataracts (41) or for epikeratophakia in congenital and traumatic cataracts (42). Koenig and cols (37) examined five adult patients who received donor corneae of 3-month olds or less which showed an induced myopia which was attributed to the high refractive power of infantile corneae. The average pre-op spherical refraction was of +1.67 D which, after the intervention, changed to negative refraction values with a mean of -7.35 D, involving a myopia of
approximately 8 dioptres. All cases exhibited a marked corneal curvature with a mean value of 57.67 D. In this way, neonatal corneal grafts in unilateral keratoplasty would cause a marked myopic anisometropy which would make it difficult to implement correction even with eyeglasses or the adaptation of a contact lens. Even though the reduction to 0.25 mm or the elimination of the disparity in the diameter of the donor graft obtained through the endothelial side and the trephination of the receiver would, in theory, cause a reduction of the craft curvature and partially compensate the subsequent myopization and, on the contrary, could create problems in the donor/receptor apposition and in the correct application of the suture due to the unforeseeable reaction of this highly elastic tissue.

C) Clinical Problems

Although theoretically the high endothelial density of infantile corneae brings about a higher feasibility of the graft, Palay and cols (43) found a greater prevalence of immunological rejections (37%) vis-à-vis the control group (6.9%) in a series of 29 eyes in which they utilize donor corneae under 6 years of age, regardless of the age of the receiver and the diagnostic, suggesting that said response could be due to expression of higher histocompatibility antigens in pediatric tissue. Even so, the graft failure prevalence was similar to that obtained with adult tissue (6.9% in both groups). This was attributed to the fact that the greater endothelial population would counteract cellular loss after a rejection, finally allowing for a transparent graft. In this sense, in what concerns the final result in both groups, the advantages and drawbacks cancel themselves out.

In our two cases we did not have intra-op events worthy of mention during trephination or suture, and the low surgical traumatism is confirmed by the first patient maintaining an endothelial density in the graft of 4,941 cel/mm$^2$ one year after the intervention. This value is practically identical to that obtained in the pre-op mirror microscopy (4,950 cel/mm$^2$) with a slight reduction 18 months after the operation (4,300 cel/mm$^2$).

The refractive response was quite different to that found in literature in reference to the use of neonatal corneae. The most relevant observation in the post-op was the unexpected intense hypermetropization instead of the expected myopia due to the usual greater curvature of the cornea in the first months of life as indicated by reference data. In addition, the moderate post-op astigmatism also raised our attention. The first observation could be attributed to the fact that the donor cornea had those values previously (which is impossible to confirm) or that the equal diameter of the donor graft and the receptor trephination, together with the highly flexibility and elasticity of the tissue, the uniform stress of the continuous suture (excessively tight during the readjustment) caused the flattening of the graft. The low initial astigmatism could be due to the readjustment of the suture under intraop kerastocopic control and the good adaptability of the graft in the receiving tissue. Even though the hypermetropic defect (both the cylindrical and spherical components) was considerably reduced in the months following the intervention, astigmatism experienced a marked variation after removing the suture. In the first patient this was done 1 year after the operation (which raises a question mark about that conventional period) which required surgical correction by means of arcuate keratotomies and reinforcing points which achieved a considerable reduction of nearly 8 dioptres which allowed the patient to reach an excellent vision of V=1 with eyeglasses correction and uneventful adaptation to contact lenses. The second patient experienced an endothelial rejection eight months after the graft. Shortly thereafter, possibly due to faster scarification, the suture loosened and fortuitously broke, requiring an early removal after which a strong increase of the hypermetropic astigmatism was observed. In spite of the energetic (topical and systemic) treatment of the rejection, the condition became irreversible in contrast with our previous experience with keratocone cases in which remission was obtained in over 95% of cases. Even though it exhibited a slight initial remission,12 months after its appearance the diffuse edema of the graft persisted, which obviously excluded surgical correction of astigmatism with the objective of carrying out a new keratoplasty in the near future.

In the light of the above, we conclude that neonatal dormer corneal graft could give rise to a strong initial hypermetropic defect contrary to the presumed myopization indicated by the small number of bibliographic references, which seems to reduce gradually.

The moderate astigmatism achieved after continuous suture and its readjustment with intra-op...
kerastocpic control experienced a big change after removal, suggesting that the persistence of marked elasticity and adaptability of the crafts causes greater curvature and a reduction of hypermetropic due to the elimination of the uniform and balanced pressure of the suture.

As the receptors were young, the faster scarification could give rise to an early loosening of the suture.

In spite of the greater endothelial density, the risk of irreversible rejection seems higher, presumably due to a high immunogenic capacity.

In the absence of larger studies and regardless of the apparently good quality of the tissue, the utilization of neonatal and lactating corneae in penetrating keratoplasty still remains uncertain due to the unforeseeable refractive and immune response.

REFERENCES


