Ways to Improve (Visual) Outcome in Corneal Transplantation, Corneal Pathology and Astigmatism

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Voor mijn ouders
Voor Joeri

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CHAPTER 1

GENERAL INTRODUCTION

1.1 HISTORY AND EPIDEMIOLOGY OF CORNEAL TRANSPLANTATION

The first visually successful penetrating corneal transplantation in human was, as far as we know, performed exactly 100 years ago by Eduard Zirm.[1] In a Moravian (Slovakia) hospital Zirm performed two penetrating keratoplasties (PKP) on a 45-year old patient who had been bilaterally blinded by a lime injury. Two small fresh corneal grafts were derived from one enucleated eye of an 11-year old boy whose eye was injured by an intraocular foreign body. The corneal graft on the right eye of the patient failed. However, the left corneal transplant remained clear and a visual acuity of 6/36 was noted after one year.[2] Great advances in surgical instrumentation and techniques and the introduction of antibiotics and corticosteroids over the second half of the last century, significantly improved the success rate for corneal transplantation. In fact corneal transplantation is at present the most widely practised form of clinical transplantation. In the UK 2329 corneal transplantations were performed in 2003, in comparison with 1697 renal transplantations.[3] Approximately 46000 corneal transplantations are performed every year in the USA.[4] Also in the Netherlands corneal transplantation is commonly performed with 642 transplantations in 2003, compared to 388 renal transplantations.[5] Although corneal transplantation is the most performed transplant, it is arguable whether it is the most successful in the long-term.

1.2 ANATOMY OF THE CORNEA AND THE REFRACTIVE SYSTEM

Anatomy

The total refractive power of the eye is about 58 diopters (D). The cornea provides 80% of this refractive power and functions as a protective membrane. From anterior to posterior it has five layers: the epithelium, Bowman's membrane, the stroma, Descemet's membrane and the endothelium. The stroma accounts for 90% of the thickness of the cornea and consists of collagen fibers, precisely arranged thus as to preserve transparency, supported by scattered keratocytes. The maintenance of normal corneal hydratation, thickness and transparency is the responsibility of the endothelium.[6]

Endothelium

The corneal endothelium is a monolayer of cells derived from the neural crest during embryologic development. Human endothelial cell density is approximately 6000 cells/mm^2 during the first month of life, but decreases to 3500 cells/mm^2 by the age of 5 years.[7,8] There is no evidence that human

endothelial cells divide under normal circumstances.[9] During life, there is a gradual loss of cells at an average rate of 0.6% a year.[10] Corneal transparency could be maintained with a density as low as 500 cells/mm^2.[11] Accelerated loss of cell density can be seen after intraocular operations.[12] After an initial decline in cell density, a gradual loss of endothelial cells at an average rate of 2.5% per year is reported after extra capsular cataract extraction.[12] After transplantation there is a rapid loss in cell number, initially due to surgical trauma and early postoperative inflammation.[13] The average rate of postkeratoplasty endothelial cell decline is shown to be 7.8% during the first 3 to 5 years[14] and 4.2% per year from 5 to 10 years.[13] Increased cell loss can be observed during a rejection reaction.[15] In some cases this results in transparency loss of the cornea and subsequent graft failure. Moreover, chronic endothelial cell loss can lead to decompensation of the graft (called slow endothelial decompensation). This is possibly the leading cause of graft failure after the first five postoperative years.[13] Thus, the long-term success of corneal transplantation depends on transplanting an adequate amount of functioning donor endothelium. Important reasons for not using donor corneas for transplantation are an endothelial cell count fallen below the arbitrary density of 2200-2300 cells/mm^2, an irregular cell mosaic or an abnormal amount of cell loss during preservation.[16,17]

Progressive endothelial cell loss is also a long-term concern after phakic intraocular lens (IOL) implantation.[18] Severe endothelial cell loss is seen in eyes with phakic angle supported IOLs.[19,20] This could possibly lead to corneal decompensation in a substantial number of eyes. In the iris-claw phakic IOL the expected amount of endothelial cell loss is probably lower due to the firm iris fixation without contact with the angle.[21] In highly myopic eyes corrected with an iris-claw lens, Menezo et al. reported an endothelial cell loss of 3.0% at 6 months, 5.5% at 1 year and 10.5% at 5 years.[22] These percentages resemble those found after cataract extraction with IOL placement in the capsular bag.[12] In hyperopic eyes with phakic IOLs long-term endothelial cell loss might be a potential problem since a negative correlation was seen between endothelial cell loss, anterior chamber depth and thickness of the IOL.[18,23]

Refractive system

Emmetropia is the optical condition in which parallel rays of light from a distance object are brought to focus on the retina by an eye with relaxed accommodation. In ametropia a disparity consists between the refractive power of the eye and the length of the eye. In myopia the optical power is too high for the axial length and in hyperopia the optical power is not enough.[24] The formation of a clear image in an ametropic eye could be achieved artificially with help of a concave

lens in case of myopia and by a convex lens in case of hyperopia. A spectacle lens alters the size of the retinal image of a distant object, particularly in higher ametropia. Contact lenses are an alternative that reduces image magnification and minification.

Astigmatism

Astigmatism is the optical condition in which the refracting power of the eye is not the same in all meridians. Parallel rays of light do not focus at a single point. In regular astigmatism the refractive power changes gradually form one meridian to the next by uniform increments.[25] Regular astigmatism can be corrected by a cylindrical lens. In irregular astigmatism, irregularities exist in the curvature of the meridian. In the terminology of astigmatism, 'with-the-rule' astigmatism refers to the condition in which the vertical meridian is the steepest. In 'against-the-rule' astigmatism the horizontal meridian is the steepest. Conventionally, the astigmatic component of refraction is written as a cylinder and an axis. This format may characterize a single refraction but is not suited to statistical analysis. Calculating average astigmatism or surgically induced astigmatism requires conversion of the polar coordinates (cylinder and axis) to a Cartesian coordinate system.[26] The angles of astigmatism must be doubled so that 0 and 180 degrees are equivalent in order to apply conventional geometry and trigonometry. For conversion of a cylinder and axis to Cartesian coordinates, the following formula should be used:

$$x = \text{Cylinder} * \cos(2 * \text{axis})$$
$$y = \text{Cylinder} * \sin(2 * \text{axis})$$

Where x is the horizontal component and y is the vertical component. The cylinder magnitude is given in diopters. Once all data are converted standard descriptive statistic formulas can be applied. Cartesian coordinates can be converted back to standard polar notation for astigmatism according to the following formula:

$$\text{Cylinder} = \sqrt{(x^2 + y^2)}$$
$$\text{Angle} = 0.5 * \arctan(y/x),$$

If $x \& y > 0$ Axis = angle
If $x < 0$ Axis = angle + 90
If $x > 0 \& y < 0$ Axis = angle + 180

Refractive data must be adjusted for vertex distance before comparison to keratometric data.

1.3 INDICATIONS FOR CORNEAL TRANSPLANTATION

Improvement of vision is the usual indication for corneal transplantation. However, preservation of the globe, cosmetic appearance of the eye and reduction of pain due to corneal pathology are other indications dealing with different outcome measurements. Depending on the geographic location, type of institution and time, indications for corneal transplantation vary.[27-34] Leading indications for keratoplasty reported by published studies from Europe, North America, Australia and New Zealand are pseudophakic bullous keratopathy, keratoconus, regraft and Fuchs' endothelial dystrophy. Other less common indications are keratitis, including herpetic keratitis, other corneal dystrophies and degenerations, chemical burns and trauma.

1.4 CORNEAL GRAFT SURVIVAL

Corneal transplantation can be a successful procedure. A success rate in excess of 90% is reported in uncomplicated cases.[35-38] Among the most common causes for transplant failure are irreversible rejection, late endothelial decompensation, ocular surface disease, glaucoma and astigmatism.[37,39] In general topical corticosteroids are given after corneal transplantation as the sole rejection prophylaxis. The ability of the corneal graft to survive in the absence of systemic immunosuppression led to the proposition that the cornea is an immune privileged tissue at an immune privileged site.[40]

1.4.1 Immunology of corneal transplantation

Several mechanisms attribute to the corneal immune privilege, and still more explanations for this phenomenon derived from animal models of keratoplasty are to be expected. Known mechanisms for immune privilege in the normal cornea thus far are:

1) Lack of both afferent lymphatic and efferent blood vessels. There is a separation of ocular tissues and the intravascular space that is referred to as the blood-ocular barrier.[41-44] The avascularity of the cornea contributes to a suppression of the afferent and efferent arm of the immune reflex arc, which could preclude transplant rejection.

2) Lack of MHC-II$^+$ antigen presenting cells (Langerhans cells) in the centre of the cornea.[45-47] This feature is explained in more detail in section 1.4.2.2.
3) Anterior chamber associated immune deviation (ACAID) directed at for example graft antigens. Intracameral injection of alloantigens results in an altered form of immunity to that antigen. This is a tolerogenic form of immunity with a selective suppression of T cells mediating delayed type hypersensitivity to antigens and suppression of complement fixing antibodies.[48-50]
4) Secretion of immunosuppressive molecules by corneal cells. These immunosuppressive molecules such as IL-1 receptor antagonist and Fas-ligand (Fas-L) have the ability to inhibit complement activation and T cells. IL-1 is a potent proinflammatory cytokine, inducing chemotaxis and activation of antigen presenting cells (APC).[51] Fas-L is expressed on the corneal epithelium and endothelium.[52-54] It is proposed that Fas-L can interact with Fas$^+$ immune effector cells (T cells) entering the eye during inflammation, inducing apoptosis of the immune effector cell without inflammatory damage.[55,56]
5) The presence of immunosuppressive cytokines, derived from the aqueous humor, such as transforming growth factor-beta-2, tumor necrosis factor-alfa, IL-10 and neuropeptides.[57-60]

1.4.2 Corneal graft rejection

Immune privilege is not absolute and can be lost due to certain circumstances. Immune rejection is an important and often the leading cause of corneal graft failure.[61-65]

1.4.2.1 Clinical diagnosis of corneal graft rejection

The diagnosis of an immune mediated graft rejection is not always clear-cut. One of the earliest signs is conjunctival and episcleral vascular engorgement, thus a general inflammatory response.[66] Corneal allograft rejection is considered when progressive clouding is seen in an until that time clear graft.[63,67] Typically edema is limited to the graft and the eye was not previously inflamed. Other signs are keratic precipitates limited to the graft and mild aqueous flare. These keratic precipitates may progress to linear accumulations on the endothelium, called 'Khodadoust rejection line'. This feature is considered a pathognomonic sign of rejection.[63] Each layer of the cornea can manifest a rejection reaction.[68] An epithelial rejection is only observed in about 10% of all rejected grafts.[63,68] This epithelial rejection is seen as an elevated line starting in the periphery and progressing towards the centre of the graft. The rejection reaction of the stromal layer is characterized by subepithelial infiltrates, which are whitish infiltrates in the anterior stroma, randomly positioned in the graft.[69] Each type of rejection

can occur concurrently with the others and separately. The endothelial rejection is the most common and has the worst prognosis since endothelial cells do not have the capacity to regenerate once affected.

1.4.2.2 Mechanism of immunity underlying graft rejection

The mechanism of corneal graft rejection is still not completely understood. To initiate a rejection reaction (afferent arm of the immune reflex arc) antigens expressed by donor tissue must be presented to recipient T cells. Two distinct forms of antigen presentation are possible. In the direct pathway, donor-derived APCs migrate out of the transplant to the recipient's lymphoid organs/tissue and stimulate directly recipient CD4+ Th cells. In the indirect pathway, recipient APCs phagocytose and express donor antigens and present them on their cell surface to naive recipient T cells.[46,70,71] Via the indirect pathway major histocompatibility class I and II antigens as well as minor histocompatibility antigens can be presented to recipient T cells. Classically this indirect route is thought to play a more prominent role in late acute and chronic rejection. The indirect pathway is more likely to be the dominant afferent route for graft rejection in non-inflamed and unvascularised corneal grafts, since APCs (MHC- II$^+$ dendritic cells) are absent in the normal cornea. The more effective direct pathway might play a relevant role in antigen presentation in vascularised or inflamed corneal grafts.[72] After T cell activation the efferent phase of the immune reflex arc starts. This is a destructive response. Fundamentally, two T cell mediated effector mechanisms can be observed in corneal graft rejection: a cytotoxic T cell (CTL) response and a delayed type hypersensitivity (DHT) response. The role of antibodies in corneal graft rejection is poorly understood and it appears that a B cell response plays no important role.[46,48,73] CD4+ T cells are the main producers for DTH response and CD8+ T cells are considered classically as CTLs. Whether corneal graft rejection is mainly dominated by a CTL or DTH response is still not clear.[74-76] Pathological examination of rejected corneal grafts has revealed a mixed cellular infiltrate compromised of both CD4+ and CD8+ T cells.[77] Animal experimental studies indicate that corneal graft rejection occurs also in mice incapable of developing CTL responses.[78] However, rejection of human transplanted corneas was found to be associated with a CTL response directed against donor HLA class I antigens.[79] Depletion of CD4+ T cells does result in a reduction of corneal graft rejection in animal models.[80,81] CD4+ T cells can be further divided based on their function in Th1 cells and Th2 cells. A DTH response is a classic Th1 immune response, characterized by preferential production of the proinflammatory cytokine interferon-gamma and IL-2. On the other hand there is evidence that some forms

of allograft rejection are Th2 mediated, since rejection is characterized by the presence of elevated Th2 cytokine expression in the inflammatory infiltrate.[82]

1.4.2.3 Influence of HLA matching on rejection

HLA antigens play a prominent role in the presentation of foreign antigens to recipient T cells. The major histocompatibility complex (MHC), in human the human leukocyte antigen system (HLA), consists of two distinct classes encoded by genes located on the short arm of chromosome 6.[83] HLA class I antigens (HLA-A, HLA-B and HLA-C) are cell surface molecules expressed on all nucleated cells. The distribution of HLA class II antigens (HLA-DR, HLA-DP and HLA-DQ) is quite different. Under normal circumstances HLA class II antigens are expressed on B-lymphocytes and on APCs like Langerhans cells in the cornea. HLA-DR and HLA-DQ are in strong linkage disequilibrium.[84] The role of HLA-DP as a transplantation antigen in corneal transplantation is quite obscure and not thoroughly investigated. HLA-A and HLA-B antigens have been identified on epithelium, stromal and endothelial corneal cells.[85-87] HLA-C is expressed at only 10% of the level of HLA-A and HLA-B, and for that reason considered as a weak transplantation antigen.[84] Expression of HLA-DR antigens carried on Langerhans cells has been demonstrated within corneal epithelium and stromal layers.[85,87] The central part of the cornea is normally devoid of Langerhans cells.[85,88] However, migration and accumulation in the central part could be established by various factors, such as vascularisation and inflammation under the influence of interferron-gamma.[89-91] Other cells that can function as APCs after migration to the cornea are monocytes and macrophages (called passenger leukocytes). Several studies have investigated the role of HLA-matching in corneal graft rejection, but there has been little consensus. Studies have produced mixed results: some studies have suggested that HLA class I matching does not play an important role in corneal graft rejection,[92] whereas others indicate that HLA class I matching results in a reduced risk of graft rejection and subsequently prolonged graft survival.[93-95] Conclusions about HLA class II matching are even more controversial with a detrimental effect found by the Corneal Transplant Follow-up study[96] and a beneficial effect found by others.[94,97,98] In Table 1 a summary of published studies to matching for HLA-A and HLA-B antigens is presented[92-97,99-101] and in Table 2 studies to matching for HLA class II antigens are summarized.[92,94,96-98,102] Comparison of the results of divers studies is complicated by different definitions of patients at high risk and various posttransplant treatment regimens. Results could further have been biased by the use of different donor preservation methods and HLA typing protocols.

1.4.3 Donor corneal storage system

With Filatov,[103] the use of cadaveric corneas for corneal transplantation instead of diseased eyes of living humans became more popular. This enhanced the supply of corneas for transplantation. A major difference between processing of donor corneas and other donor material is that the cornea does not need to be 'fresh' at transplantation. Recent advances in eye banking and corneal preservation now allow routine storage of the cornea for up to 5-6 weeks through the use of tissue-culture technique. In the Netherlands organ culture preserved donor corneas are used since 1982/3.[17] The ability to store corneas provides an enormous advantage, as it allows both scheduling of transplant surgery and allocation and quality testing of the donor cornea before grafting. A further advantage of the use of organ culture storage might be an altered immunogenicity of the donor cornea. This immunologic alteration is ascribed to the loss of 'passenger leukocytes' and the relatively hypocellularity of the donor epithelium after organ culture.[104,105] A depletion of HLA-DR bearing donor dendritic cells

Table 1. A summary of published studies to matching for HLA-A and HLA-B antigens

First author, year	No. of grafts	HLA typing	Inclusion	Event analysed	Matching effect
Sanfilipo, 1986	97	serology	high-risk	rejection and immune failure	Beneficial effect for HLA-A and HLA-B matching
Ozdemir, 1986	40	serology	high-risk	graft failure	Beneficial effect for HLA-A and HLA-B matching
Boisjoly, 1990	435	serology	mixed, majority low-risk	rejection	Beneficial effect for HLA-A and HLA-B matching, more pronounced in low-risk group
The CCTS, 1992	419	serology	high-risk	rejection and immune failure	No effect of HLA-A or HLA-B matching
Hoffmann, 1994	248	serology	mixed	rejection	No significant effect of HLA-A matching, beneficial effect of HLA-B matching in both low and high-risk group
Vail, 1997	602	not defined	mixed	rejection	Possible (not significantly) beneficial effect of HLA-A and HLA-B matching
Roy, 1997	693	not defined	mixed	rejection	No effect of HLA-A and HLA-B matching for high-risk group, beneficial effect of HLA-A and HLA-B matching for low-risk group
Morita, 1998	80	DNA	mixed	rejection	Beneficial effect for HLA-A matching for total group and high-risk group
Völker-Dieben, 2000	1189	serology	mixed	rejection and immune failure	Beneficial effect for HLA-A and HLA–B matching

Table 2. A summary of studies to matching for HLA class II antigens

First author, year	No. of grafts	HLA typing	Preservation method	Inclusion	Event analysed	Matching effect
Baggesen, 1996	74	DNA	Organ culture	high-risk	graft survival	Beneficial effect for HLA-DR matching
The CCTS, 1992	419	serology	McCarry-Kaufman/ KSOL culture medium	high-risk	rejection and immune failure	No effect of HLA-DR matching
Munkhbat, 1997	81	DNA	Optisol preservation	mixed	rejection	Beneficial effect for HLA-DP matching in high risk group, no significant effect for HLA-DR matching in either risk group
Vail, 1997	602	serology	Moist chamber/ McCarry-Kaufman/organ culture	mixed	rejection	Detrimental effect for HLA-DR matching
Völker-Dieben, 2000	558	serology	McCarry-Kaufman/organ culture	mixed	rejection and immune failure	Beneficial effect for HLA-DR matching on rejection and immune failure
Hoffmann, 1994	248	serology	Moist chamber	mixed	rejection	Beneficial effect of HLA-DR matching in both low and high risk group

is found after several days of organ culture preservation.[85,106] This depletion of Langerhans cells or macrophages in donor corneas might improve graft survival and could be considered as a contribution to the immune privilege.[107] HLA-A, HLA-B and HLA-C antigens are still present after organ culture preservation, though fewer.[85]

1.4.4 HLA typing techniques

The HLA molecules are highly polymorphic. Within one individual the chance that the MHC genes on both chromosomes will encode the same allele is small; that is most individuals are heterozygote. It is also unlikely that two unrelated individuals would be identical at all loci. The observation of a higher percentage of homozygosity than expected should raises doubt. A common error with serological typing is failing to identify a second HLA-DR locus antigen, resulting in a higher percentage of homozygosity.[108,109] In general serological typing for HLA class I is less prone to error and yields accurate broad typing results. The serological typing errors might partly be explained by the difficulty of typing peripheral blood samples from cadaver donors. A newer method of HLA typing is a technique using genomic DNA restriction fragment length polymorphism

(RFLP). Although RFLP typing yields good results for HLA-DR, this procedure is time consuming and cannot be prospectively used for typing of cadaver donors.[110,111] Recently, PCR-based DNA typing systems have become available for HLA class I and II, which are rapid, more accurate than serological typing and can define single amino acid polymorphism.[112,113] Accurate broad and split antigens for HLA class I and II can be defined by DNA typing systems. Using DNA typing techniques, approximately 25% of the HLA-DR antigens turned out to be erroneously typed by serological means.[114,115]

1.4.5 Other antigens influencing corneal graft rejection

Data derived from animal experimental studies indicate that incompatibility between donor and recipient for minor histocompatibility antigens play a role in graft rejection.[116,117] There are problems, however, with relating data from animal models of keratoplasty to the human setting. Immunologic rejection of corneas in mice and rats is more aggressive than in humans. The ABO and H-Y antigens are the most well known human minor histocompatibility antigens. Data about the role of these minor antigens in human corneal transplantation are controversial and not conclusive with respect to ABO matching.[95,118-120] Also a significant contribution of H-Y antigens to graft rejection in humans has so far not been shown.[121]

1.4.6 Predictors for corneal graft survival other than immune factors

Because rejection is a serious threat for graft failure, all risk factors for rejection are principally risk factors for graft failure. The state of the recipient cornea itself is an important factor that determines the success of the graft. This led to the proposition of high-risk recipients for corneal graft failure. In general high-risk recipients are identified by virtue of having deep stromal vascularisation or having a history of previous graft rejection. Primary grafts have a significantly better long-term survival compared with regrafts.[13,37,64,122] Vascularisation is an other important risk factor for graft survival.[37,64,123-125] Other recipient factors possibly associated with an increased risk of graft failure are a history of pregnancy or blood transfusion,[126] anterior synaechiae,[39,127] glaucoma,[36,39,65] dry eyes,[69,128] inflammation at the time of keratoplasty, especially in active herpetic infection[65] and aphakia.[36,64,65,96] The indication for transplantation is highly related to the inflammatory condition of the eye and vascularisation of the recipient bed and subsequently to graft survival. Reported graft survival rates of different studies may vary with the inclusion of variable percentages of each indication. Overall 10-year graft survival rates reported vary from 59 to 80%.[13,64,129] Survival rates for the indication of keratoconus and Fuchs' endothelial dystrophy are generally

good. For keratoconus survival rates of 92 to 95% are reported after 5 years to 10 years.[36-38] Reported graft survival rates for Fuchs' endothelial dystrophy are 61% at 4 years follow-up by Olsen et al.,[130] 89% at 8.4 years by Pineros et al.[131] and 81% and 90% at 10 years respectively by Ing et al.[13,64] and Thompson et al..[64] These high survival rates are in sharp contrast to the survival rates for herpes simplex keratitis, in particular after regrafting.[65,120]

1.5 POSTKERATOPLASTY COMPLICATIONS

Several postoperative complications can influence graft survival or postoperative visual acuity. Some of these factors are discussed.

Wound dehiscence

Erasmus Darwin wrote[132] "Could not a small piece of cornea be excised with a trephine, the size of a small bristle or a large quill and would it not heal with a transparent scar?"

It is a question whether the corneal wound after keratoplasty will ever be healed. Calkins et al. demonstrated that the strength of the graft-recipient interface is weak even 1 year after transplantation.[133] Wound abnormalities in keratoplasty include incarceration of Bowman or Descemet membrane or retrocorneal fibrous tissue sealing the wound.[134,135] The imperative wound healing exposes the patient to a significant risk of wound dehiscence and even loss of the eye, since wound dehiscence can lead to a suprachoroidal haemorrhage or endophthalmitis.[136-138] Furthermore, wound dehiscence creates an unpredictable and changing refractive error.[136] Wound dehiscence appears not to be related to specific suture technique. Binder et al.[139] reported a 5.7% incidence of spontaneous wound dehiscence after PKP using all kinds of suture techniques. However, the incidence of wound dehiscence is correlated with suture removal.[139] Wound strength without sutures remains low indefinitely after PKP. To promote wound healing and to reduce the risk of wound dehiscence and astigmatism a modification of the standard PKP could be used. In this technique a full thickness donor graft with a larger posterior diameter is used in conjunction with a peripheral lamellar wound configuration, resulting in a smaller anterior diameter of the graft.[140] Although this technique is more time consuming than a standard PKP procedure, it may be a valuable alternative for posterior corneal pathology indications such as pseudophakic bullous keratopathy and Fuchs' endothelial dystrophy.

Suture related problems

Several suture related complications can interfere with graft survival.[141] Suture loosening increases the risk of rejection.[142] Loose sutures also predispose to postoperative infection.[69] Vascularisation might be encouraged by the presence of sutures, especially by interrupted sutures.[143] On the other hand, sutures loosen especially in a vascularised recipient bed. For that reason continuous suturing in high-risk patients should be discouraged. Spontaneous suture erosion through the epithelium is a significant risk for retained sutures.[144] The risk for encountering suture related problems ends when all sutures are removed. However, suture removal is also a possible factor inducing graft rejection and as mentioned before wound dehiscence.[141]

Astigmatism

A clear graft will not result in good vision if the optical properties of the cornea are inappropriate. The leading cause of poor vision in an otherwise clear corneal graft is astigmatism.[65,145,146] Postoperative corneal astigmatism decreases with increasing graft size.[147] However, larger grafts are shown to be associated with a higher risk of rejection.[124,126,148] Malposition of donor and recipient cornea, irregularities in trephination and uneven suture tension are important causes of astigmatism after keratoplasty.[149,150] Despite newer techniques and instruments, mean astigmatism after PKP ranges between 2.5 and 3.5 D with more than 40% of cases having an astigmatism greater than 3.0 D.[131,151,152] Surgical techniques proposed to prevent or reduce astigmatism in corneal transplantation are numerous. There is no common agreement about which suture technique is the best for astigmatism control. Adjustment of a continuous suture or selective removal of interrupted sutures are widely adopted techniques to reduce postoperative astigmatism.[151-155] The effect of selective suture removal, however, is lost after all sutures are removed and the advantage is apparent only in the first years after transplantation.[156] Furthermore, suture removal any time after transplantation can result in unpredictable and large changes in astigmatism.[157-159] A non-biodegradable suture that can be left in place permanently without loosening could contribute to a better astigmatism control.

If optical correction of the astigmatism is required, the first option is spectacles, the second is contact lenses. If what can be achieved with optical devices is not acceptable for the patient, several surgical options are available to improve visual performance. Some of them will be discussed in the following sections.

1.6 ALTERNATIVES TO PENETRATING KERATOPLASTY

Given the numerous side effects in corneal transplantation and restricted long-term graft survival, other treatment modalities than PKP could be preferred in an attempt to delay or avoid PKP. The possible alternatives vary among the indication for transplantation.

1.6.1 Posterior lamellar keratoplasty or deep lamellar endothelial keratoplasty

Posterior lamellar keratoplasty (PLK) and deep lamellar endothelial keratoplasty (DLEK) are basically two terms for the same procedure.[160,161] This procedure can be used for the treatment of endothelial corneal pathologies, mainly pseudophakic bullous keratopathy and Fuchs' endothelial dystrophy. The philosophy is to selectively replace the diseased layer and to leave the healthy tissue intact. Advantages of PLK compared to PKP are less induced astigmatism and no need for sutures with associated problems. Although results of PLK are promising, this is still a procedure in development and long-term results remained to be seen.

1.6.2 Anterior lamellar keratoplasty

Indications for this procedure can be keratoconus or opacifications in the anterior to mid stroma of the cornea. Advantages of lamellar keratoplasty (LK) compared to PKP are preservation of the recipient endothelium, reduced risk for graft rejection, better wound stability and less need for corticosteroids.[162] Interface scarring and irregular astigmatism are the main problems limiting postoperative visual acuity in LK. Optical results are generally better with PKP than with LK. With a newer technique of deep lamellar keratoplasty (DLK) the limitations of conventional LK might be decreased.[163] However, DLK is more difficult and carries the risk of Descemet's membrane perforation.[164]

1.6.3 Non keratoplasty procedures

If the cornea is still transparent in an eye with keratoconus or marginal degeneration, other surgical options besides PKP or LK could be considered. These options are mainly aimed at the reduction of astigmatism in patients who are contact lens intolerant. Options such as photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK) remain limited as keratoconus and marginal degeneration are considered as contraindications because of poor refractive stability and the risk of progressive ectasis.[165,166] Epikeratoplasty could be regarded as an alternative to LK. The aim of this procedure is to flatten and stabilize the ectatic cornea.[167] Optically PKP is found to be superior to epikeratoplasty.[168] Corneal wedge resection have been used in keratoconus and marginal degen-

Table 3. Summary of studies correcting astigmatism with intrastromal ring segments in eyes with keratoconus

Author, year	n	rings	Follow-up (months)	Preop mean SE (D)
Colin, 2001	10	intacs	12, all eyes	NR
Boxer Wachler, 2003	74	intacs	mean 9	-3.89±5.16
Siganos, 2002	26	FICR	6, all eyes	-6.91±5.02
Kwitko, 2004	51	FICR	mean 13	-6.08±5.01

SE, spherical equivalent; BSCVA, best spectacle corrected visual acuity; PKP, penetrating keratoplasty; NR, not reported; FIRC, Ferrara intracorneal ring (segments)

eration with variable results.[169-172] Poor predictability and limited improvement in visual acuity with this procedure have precluded widespread use.

1.6.3.1 Intracorneal rings

Previously intrastromal rings were used to correct low myopia. Recently, the use of these rings is evaluated in patients with keratoconus and early marginal degeneration.[173-177] The goal of the treatment with intrastromal rings is to reshape the cornea: astigmatism might be reduced or irregular astigmatism might be changed towards more regular astigmatism. Two types of rings are available: Intacs corneal rings and Ferrara intracorneal ring segments (FICR). Differences between these rings are a more centrally placement and a triangular anterior shape of the FICR compared to a flat anterior shape of the Intacs. A summary of published studies on corneal rings for keratoconus is listed in Table 3. Although spherical equivalent error and astigmatism were significantly reduced in all studies after implantation of the ring segments, the predictability was moderate. Besides, stability of refraction and visual recovery after segment placement were not optimal with an ongoing decrease of refractive astigmatism during the first year, as shown by Colin et al..[174] Unacceptable visual side effects such as glare and halo could occur. Extrusion of a segment with subsequent bacterial keratitis as reported by Kwitko[175] is a serious complication. It is yet not known whether intracorneal rings accelerate the progression of corneal ectasia or stabilize the situation. Intacs might also be used for early pellucid marginal degeneration. Kymionis et al.[173] report on a successful case: best spectacle corrected visual acuity improved from 20/50 to 20/25 and refractive cylinder decreased from –8.50 D to –5.50 D. In advanced stages of the disease, however, it might be impossible to implant the segments, because of progressive thinning of the inferior cornea. For patients with keratoconus and marginal degeneration also combined surgical

Postop mean SE (D)	Preop mean Cyl (D)	Postop mean Cyl (D)	Postop mean BSCVA	Explantations or PKP during study (%)
NR	4	1.3±1.4	0.63	not included
-1.46±4.11	NR	NR	0.63	5.4%
-1.11±2.56	4.42±2.23	2.20±1.02	0.60	7.7%
-4.55±5.71	3.82±2.13	2.16±2.07	0.44	25.5%

procedures could be considered in cases with irregular astigmatism and a high degree of myopia: intrastromal rings plus a phakic IOL.

1.6.3.2 Phakic intraocular lenses

Toric iris-fixated phakic IOLs can be considered for the reduction of anisometropia and astigmatism after penetrating keratoplasty.[178,179] The use of phakic IOLs for the correction of myopia and astigmatism in patients with keratoconus and marginal degeneration is evaluated in this thesis (chapter 5 and 6).

1.7 REFRACTIVE SURGERY FOR AMETROPIA AND ASTIGMATISM IN EYES WITHOUT FURTHER PATHOLOGY

The primary goal of refractive surgery is to establish a permanent correction of the refractive error in order to make the patient contact lens or spectacle independent. Moreover, a superior quality of vision is critical, since patients for refractive surgery typically have no further ocular pathology. To compare refractive results of different studies it is essential that refractive data be reported in a consistent manner. The following elements are mandatory: safety, efficacy, predictability and stability.[180] Safety can be expressed as percentage of eyes loosing one, two or more lines of best spectacle corrected visual acuity (BSCVA). The safety index is the ratio of mean postoperative BSCVA over mean preoperative BSCVA. Efficacy can be described as percentage of eyes with uncorrected visual acuity (UCVA) of 20/20 or 20/40. This outcome measurement is less informative when amblyopic eyes are involved. Efficacy index is the ratio of the mean postoperative UCVA to the mean preoperative BSCVA and might be more informative. The accuracy of the refractive treatment is addressed by the predictability. Postoperative spherical equivalent (SE) could be given together

with percentage of eyes within 1.00 D and 0.50 D of attempted postoperative refraction. Spherical equivalent is not an appropriate measure of surgical success in eyes with high astigmatism. Vector analysis should be used to calculate mean astigmatism and surgically induced astigmatism. The method for vector analysis of astigmatic data is given before. Stability should be given by showing SE refraction or change in astigmatism throughout the postoperative period.

Several surgical techniques for the correction of moderate to high ametropia combined with astigmatism are available. Indications for and advantages and disadvantages of different techniques are listed below.

PRK

Photorefractive keratectomy (PRK) offers good results in low to moderate myopia. To increase predictability of higher myopic corrections, multizone ablation techniques and scanning laser beams have been developed.[181] Ablation depth could be reduced by the multizone technique. Hyperopic treatments require larger ablation diameters than myopic treatments. Hyperopic PRK appears to be relatively safe and effective for corrections up to +4.00 D.[182-184] In the Netherlands, the advised upper treatment limit for myopia is –8.0 D.[184] Higher myopic or hyperopic corrections, however, showed poor predictability (under and over corrections) and an increased risk of complications such as corneal haze and corneal irregularities.[184-187] Loss of BSCVA may arise from these complications. As shown in Table 4, more than 10% of treated eyes lost two or more lines BSCVA.[186-188] Another problem with correction of high myopia and hyperopia is regression.[184,186,188]

LASIK

Laser in situ keratomileusis (LASIK) can treat a wide range of myopia. However, with increased amount of myopia, predictability, efficacy and stability decrease. Results are significantly worse in high myopia (> 7 D) compared to lower

Table 4. Recent studies on moderate myopic and hyperopic astigmatism corrections with PRK

Author, year, Laser	n	Follow-up (months)	Preoperative mean SE or S & C (D)	% ± 0.50 D	% ± 1.00 D	Loss BSCVA ≥ 2 lines
Hersh, 1998, Summit	68	6	SE -9.3 (range: -6.0 to -13.9)	29.4%	57.4%	11.8%
Nagy, 2002, Meditec Mel 70G	38	12	S: +3.56 and C: +2.64	42%	63.2%	15.8%
El-Agha, 2003, VISX S2	41	9	SE +3.06, C: +1.31	NR	80%	10.0%

SE, spherical equivalent; BSCVA, best spectacle corrected visual acuity; NR, not reported

myopia.[189-191] Furthermore, the correction that can be treated is limited by the amount of tissue, which has to be removed. A generally held minimum residual corneal bed thickness of 250µm remains a structural barrier to larger optical zones and thus higher corrections. A thinner residual corneal bed may lead to corneal ectasia, although the critical corneal thickness to avoid ectasia is not clear.[192,193] In general a corneal thickness less than 500µm is a contraindication for LASIK.[182] Although haze appears to be a minor problem after LASIK in comparison with PRK, other complications such as irregular corneal surface, decentration and induced astigmatism, can cause loss of BSCVA.[186] After myopic LASIK the improvement in BSCVA appears to be less compared to after phakic IOL implantation. This phenomenon of gain in BSCVA is attributed to the image magnification inherent to correcting myopia closer to the eye's nodal point.[194] The incidence of regression of more than 1 D after LASIK in eyes with moderate to high myopia has been shown to be almost 40%.[195,196] It is difficult to compare different studies because of variations in the range of preoperative myopia and astigmatism, type of lasers and follow-up time. A summary of recently published studies on moderate to high myopic LASIK is presented in Table 5.[186,189-191,197-200] Results of LASIK for hyperopia and hyperopic astigmatism (Table 6) are generally worse compared to results for myopia. It is easier to flatten the central cornea

Table 5. Recently published studies on the treatment of moderate myopia with LASIK

Author, year, Laser	n	Follow-up (months)	Preoperative mean SE or S & C (D)	% ± 0.50 D	% ± 1.00 D	Loss BSCVA ≥ 2 lines
Hersh, 1998, Summit	61	6	-9.23 (range: -6.0 to -14.4)	27.1%	40.7%	3.2%
Steinert, 1998, Summit	68	12	-9.2 (range: -6.0 to –12.0)	23%	54%	2%
Knorz, 2000, Keracor	89	3	S -7.83 (range: -6.1 to –12.0) & C –1.06 (range: 0 to –3.5)	75%	NR	5%
FDA, 2000, Nidek	322	6	>-7.0	43.4%	73.3%	3% [a]
FDA, 1999, Summit		6	>-7.0	61.3% [b]	83.9% [b]	3.3%
Sanders, 2003, VISX S2	559	6	-9.1 (range: -8.0 to –12.0)	53%	76%	2%
Reviglio, 2000, Lasersight 200	100	6	range: -6.0 to -25.0	68.4%	85.1%	0%
FDA, 1998, Kremer	248	6	>-7.0	42.3%	62.5%	6.4%

SE, spherical equivalent; BSCVA, best spectacle corrected visual acuity; NR, not reported
[a] result at 12 months; [b] including also low myopia group (<7.0 D)

Table 6. Recently published studies on the treatment of moderate hyperopia or hyperopic astigmatism with LASIK

Author, year, Laser	n	Follow-up (months)	Preoperative mean SE or S & C (D)	% ± 0.50 D	% ± 1.00 D	Loss BSCVA ≥ 2 lines
Goker, 1998, Keracor	54	6	+6.5 (range: 4.25 to 8.0)	42.6%	81.5%	5.5%
Lian, 2002, Technolas 117C	59	6	+3.12 (range: 1.0 to 5.75)	55.6%	81.5%	1.9%
Salz, 2002, LADARVision	143	6	S +3.65 (range: 1.0 to 6.0) & C-1.62	60.5%	88.7%	5.8%
Arbelaez, 1999, Keracor 117C	14	12	range: +3.10 to +5.00	NR	58%	14%
	13	12	range: +5.10 to +9.50	NR	17%	15%

SE, spherical equivalent; BSCVA, best spectacle corrected visual acuity; NR, not reported

permanently for myopia than to steepen it centrally for hyperopia.[184] LASIK has been shown to be very effective and predictable in lower hyperopia up to 3 D.[201] There is no general agreement about the upper limit of dioptric correction. However, above approximately 4 to 5 D, efficacy, predictability and stability falls off markedly.[202-205] Significant regression has been reported in LASIK for hyperopia, being strongly associated with the magnitude of hyperopia.[205] Goker et al.[206] reported 42% of enhancements to achieve the reported results in Table 6. Safety is another concern in LASIK for moderate hyperopia. Arbelaez and Knorz[207] found considerable loss in BSCVA in a group with higher hyperopia. They advise against LASIK in these eyes.[207] Decentration seems to be a particular risk with hyperopic LASIK. This problem is compounded by the typically small size of hyperopic eyes, the prerequisite for a large ablation zone and problems with fixation in possibly amblyopic eyes. Many hyperopic patients are not good candidates for hyperopic LASIK because of their morphologically different eyes.

Clear lens extraction/refractive lens exchange

Posterior toric IOL implantation after clear lens extraction (CLE), also called refractive lens exchange, is another option to correct both ametropia as well as astigmatism.[208] Clear lens extraction, however, will result in permanent and complete loss of accommodation in relatively young patients. Furthermore, CLE carries a risk for retinal detachment.[209,210] Rotational stability might be a problem with toric IOLs in the capsular bag.[208] With a toric plate haptic design lens rotational stability appears to be better, although axis misalignment of 10 or more degrees was reported in 28% of cases.[211] Probably the best candidates

for CLE are patients with high hyperopia, shallow anterior chambers and convex irises, who are neither good candidates for phakic IOL implantation nor for excimer laser correction.

1.7.1 Phakic intraocular lenses

Implantation of phakic IOLs to correct high myopia started already in the 1950s, developed by Strampelli and Barraquer.[212] The implantation of a phakic IOL might increase the risk of a retinal detachment, although this risk appears to be lower than after lens extraction.[209,213] The expected incidence of a retinal detachment in phakic myopic eyes (>-10 D) without previous surgery is estimated to be 0.68% per year.[214] It is not clear whether prophylaxis treatment with argon laser influences the risk of a retinal detachment.[210]

1.7.1.1 Angle supported anterior chamber intraocular lenses

Angle supported anterior chamber IOLs are dependent on the size of the anterior chamber. A 'white to white' (horizontal corneal diameter) measurement is performed to determine the necessary size of this phakic IOL. Implantation of the haptics in the correct position at the angle and implantation of the correct lens size are essential to prevent complications.[213] Pupil ovalisation is a frequent encountered complication related to an oversized lens.[212,215] A small phakic IOL can rotate and decentrate, and produces complains of halo and glare. First generation angle-supported phakic IOLs were associated with high endothelial cell loss. This appears to be less in newer designs, which can be implanted through a small incision, although long-term results are not yet available. Despite the newer designs, pupil ovalisation remains a problem.[212,215] To my best knowledge no studies have been published on a toric version of angle-supported IOLs thus far. A potential problem with toric angle-supported lenses is rotational stability.[216]

1.7.1.2 Posterior chamber phakic intraocular lenses

Two types of posterior chamber phakic intraocular lenses (PCPIOL) are commercially available: the silicone phakic refractive lens (PRL)[217] and the collamer implantable contact lens (ICL).[218] Predictability and efficacy of the PCPIOLs have been shown to be very reasonable and superior to LASIK for myopia between –8 and –12 D.[199] Percentage of eyes within 1.00 and 0.50 D of attempted correction for high myopia as reported by two different studies is presented in Table 7.[217,219] Risks reported in PCPIOLs are cataractogenesis and pigment dispersion.[220-224] In hyperopic eyes there might be a significant higher risk of developing a pupil block glaucoma.[225] However, the advantage of a PCPIOL in a hyperopic eye

Table 7. Predictability of high myopic correction with PRL or ICL

PCPIOL type	Preoperative myopia (D)	% ± 0.50 D	% ± 1.00 D
PRL	≥ -10.50	44%	79%
ICL	> -10.00	56.9%	80%

PCPIOL, posterior chamber phakic intraocular lens; PRL, phakic refractive lens; ICL implantable collamer/contact lens

might be a greater distance between the lens and the endothelial layer, compared to an anterior chamber IOL. Although a toric version of the myopic ICL is available, published studies with the exception of one case report, describe only refractive results for the correction of moderate to high ametropia without astigmatism.[224-227] Gimbel et al.[228] report satisfactory results of the correction of high myopia and astigmatism in one eye with a toric ICL. A prospective study has started recently with the purpose to evaluate the safety and efficacy for the treatment of myopic astigmatism with a toric PCPIOL.[229]

1.7.2 The Artisan lens

In 1978 Professor Worst designed the iris-claw lens for the correction of aphakia. In 1980 a modification of this iris-claw lens was used in a phakic eye as an occlusive lens for treating acquired diplopia.[230] Also years after implantation the cornea and crystalline lens of this eye remained clear.[230] Worst and Fechner modified the existing iris-claw lens into a negative biconcave lens for the phakic eye, which was implanted for the first time in 1986 to correct high myopia.[231,232] In 1991 the optical part of the lens was altered into a convex-concave model with a larger optical zone of 5.0 mm to reduce photopic phenomena.[233,234] In 1998 the name of the lens was changed to the Artisan lens. Toric Artisan lenses for the correction of both ametropia and astigmatism are commercially available since 2000. The biomaterial of the toric Artisan lens consists of Perspex CQ-UV polymethylmethacrylate with ultraviolet filtration. Its overall diameter is 8.5 mm and the optical zone diameter is 5.0 mm. The toric Artisan lens is available in half diopter increments with a cylindrical power up to 7.5 D and a spherical power from –3.0 to –23.5 D for myopia and from +2.0 to +12.0 D for hyperopia. Two models of toric phakic Artisan lenses are available to allow the preferred approach and optimal implantation on the correct axis. In Model A, the axis runs through the claws at 0º and in Model B, at 90º. The necessary power of the lens can be calculated with the Van der Heijde formula.[235] Required data for lens calculation are: subjective refraction, anterior chamber depth and keratometry. To achieve precise placement of the IOL in the correct cylinder axis, the enclavation sites should be marked prior to surgery. Exact enclavation of the lens is

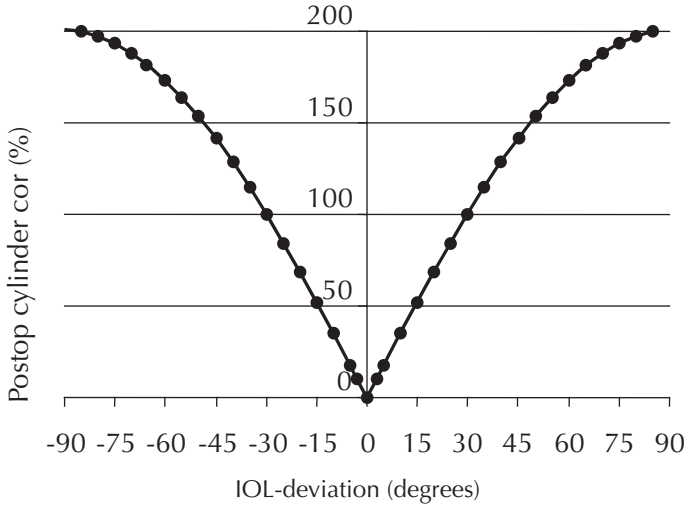

Figure 1. Effect of lens rotation on postoperative cylinder correction.

paramount. Especially in higher degrees of astigmatism, minimal misalignment greatly reduces the corrective value of the lens. Approximately one third of the cylindrical correction is lost if the lens is rotated 10 degrees off axis, as illustrated in Figure 1. To be correct, marking must be done under binocular circumstances in a sitting position, without immobilization of the eye by anaesthetics. Different techniques could be used for marking the enclavation site: 1. Surface markers, which mark at the limbus or cornea, guided by a gravitation marker or by the reflex of the Javal keratometer, 2. Marking of the iris can be done by either YAG or Argon Laser,[236] 3. Natural reference points in the iris using a digital photograph or drawing could also guide to the axis of enclavation.

It is not possible to implant the Artisan toric lens through a smaller than 5.2 - 5.3 mm incision. Any induced astigmatism by the incision might influence accuracy of postoperative refraction. The clinical outcome of the toric Artisan lens for the correction of moderate to high myopia combined with astigmatism and for the correction of moderate to high hyperopia with astigmatism was investigated and results are described in chapter 7 and 8.

1.8 AIMS OF THE THESIS

Corneal transplantation can be a successful procedure. Despite a certain immune privilege of the cornea, technological refinements in surgical procedures, organ culture storage of donor corneas and the use of corticosteroids after

transplantation, allograft rejection is still a leading cause of graft failure. The risk of rejection is increased in patients having deep stromal corneal vascularisation or a history of previous graft rejection (so called high-risk patients). Disparity between donor and recipient at the HLA locus is the predominant basis for graft rejection in other organ transplantations. It might be expected that corneal graft survival in high-risk cases would increase after prospective HLA matching of donor and recipient. Nevertheless, allocation of donor corneas based on HLA matching has been a controversial topic for several years. Nowadays it is possible to determine HLA matches more accurate and precise. The objective of the studies described in chapter 2 and 3 was to assess the effect of HLA matching on immune mediated graft rejection and failure using modern HLA typing techniques. Results of these studies might be of help in setting up guidelines for allocation of donor corneas. Besides by HLA matching, the outcome of corneal transplantations could be improved by preventing suture related problems and reducing astigmatism. The standard suture material used for corneal transplantations is Nylon (10.0 or 11.0). This material biodegrades and may loosen over time. This feature can be associated with high astigmatism, wound dehiscence, infiltrates, microbial keratitis and rejection. Mersilene is a non-absorbable suture material. The study described in chapter 4 compares the use of Mersilene sutures with Nylon sutures, with regard to astigmatism control and suture related complications.

Long-term graft survival is always worse compared to short-term graft survival. Restricting the necessarily graft survival time by delaying transplantation might be beneficial to a patient. If the primary indication for transplantation is high astigmatism in a contact lens intolerant patient, other treatment modalities than PKP could be considered, with the purpose of reducing astigmatism. Recently, a toric version of the Artisan iris-claw lens has become commercially available. In chapter 5 and 6 we report on the results of correcting high astigmatism due to corneal pathology (marginal degeneration and keratoconus) with the toric Artisan lens.

Refractive surgery is gaining widespread acceptance. Many of the refractive surgery procedures permanently and irreversibly alter corneal shape. LASIK and PRK have shown their limitations for high refractive errors in order to prevent iatrogenic corneal pathology requiring a subsequent transplantation. In the search for a reliable refractive solution for high ametropia, phakic IOLs have become increasingly popular. The toric Artisan lens is designed to achieve full correction of both high ametropia and astigmatism in one procedure. The purpose of the studies described in chapter 7 and 8 was to assess safety, efficacy and predictability of toric Artisan lenses in the correction of high ametropia combined

with astigmatism with an emphasis on IOL axis misalignment and incisionally induced astigmatism in chapter 7.

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CHAPTER 2

INFLUENCE OF HLA-A, HLA-B, AND HLA-DR MATCHING ON REJECTION OF RANDOM CORNEAL GRAFTS USING CORNEAL TISSUE FOR RETROSPECTIVE DNA HLA TYPING

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ABSTRACT

Aim: To establish if coincidental HLA-A, HLA-B, and HLA-DR tissue matching is associated with a reduced likelihood of corneal graft rejection.

Methods: Organ culture preserved random donor corneas were used for penetrating keratoplasty (PKP). Corneal tissue from all graft recipients and donors or blood samples from recipients after repeated transplantation were obtained in order to perform retrospective molecular HLA typing. A group of 21 recipients with a rejection episode (cases) after corneal transplantation was compared with a control group of non-rejectors (n = 43). 31 graft recipients were considered as high risk patients. The influence of HLA-A, HLA-B, and HLA-DR matching on rejection free graft survival time was analysed with Kaplan-Meier statistics and Cox regression.

Results: A prolonged rejection free survival time was observed in graft recipients with one or two HLA-A matches (log rank test, p = 0.034). This effect was also observed in high risk graft recipients with one or two HLA-DR matches (log rank test, p = 0.030).

Conclusions: Coincidental HLA-A and HLA-DR matches were observed and associated with a prolonged rejection free survival time in the total group and in the high risk group, respectively. These results support the beneficial effect of prospective HLA-A and HLA-DR typing upon corneal graft survival.

INTRODUCTION

Corneal grafting is often a successful procedure.[1] In contrast with transplantation of other solid organs, no systemic immunosuppressive agents are needed to prevent allograft rejection.[2] In avascular corneas, graft survival results of 85-95% were reported after 1 year of follow up.[1,3] Nevertheless, immunological allograft rejection is reported to be the leading cause of corneal graft failure.[3,4] The incidence of immune mediated graft rejection and failure is increased in high risk patients, having corneal vascularisation or a history of graft rejection.[5-8] It might be expected that corneal graft survival in high risk cases would increase after prospective human leukocyte antigen (HLA) class I matching of donor and recipient,[5,9-12] in accordance with HLA matching for increased graft survival of other solid organs.[13,14] However, the role of HLA matching in reducing corneal graft failure could not be confirmed by all studies.[3,15-18] A beneficial role of HLA-A and HLA-B matching can be explained by the finding that mismatched HLA class I antigens are immunogenic.[19,20] HLA class I antigens are targets for rejection by CD8+ cytotoxic T lymphocytes.[21]

Organ culture preservation of donor corneas was shown to contribute to a reduction in the amount of HLA class II bearing Langerhans cells,[22-24] resulting in reduced antigenicity of the corneal graft.[19,25] This may lead to a decreased incidence of rejection. HLA-DR (class II) matching in cornea transplantation showed beneficial effects[26,27] and an adverse effect in another study.[28] This controversy may be explained partly by inadequacy of serological HLA-DR typing techniques.[29]

Although HLA matched corneal grafts were rarely used in patients at high risk of rejection at the University Medical Centre of Utrecht, Netherlands, a relatively high success rate of corneal transplants was observed over the last 5 years.[30] With the recent availability of DNA based typing techniques[29,31,32] it is possible to perform HLA-A, HLA-B, and HLA-DR typing of recipients and donors retrospectively and accurately.[33-36]The aim of this retrospective study was to examine whether differences exist with regard to molecular HLA-A, HLA-B, and HLA-DR matching and to rule out coincidental HLA matching between corneal graft recipients, with versus without immune mediated graft rejection.

PATIENTS AND METHODS

Patients

Between February 1995 and December 1997, 248 consecutive patients underwent PKP with random corneal grafts at the University Medical Centre of Utrecht, Netherlands. Patient charts were revised for age, sex, use of systemic immune suppression, a history of glaucoma or herpes simplex keratitis (HSK), tear film insufficiency, number of previous grafts, indication for transplantation, degree of stromal vascularisation of the recipient cornea at the time of PKP, additional surgical procedures during PKP, any rejection episodes, and the final outcome of the corneal graft. In the category of patients with a history of glaucoma we included patients with ocular hypertension or primary open angle glaucoma (POAG) based on use of antiglaucoma medication, neuropathy with an excavation of the optical nerve, defects in the visual field, a diagnosis of POAG or an intra-ocular pressure above 23 mm Hg. Furthermore, information about the donors and donor corneas was collected; age, sex, graft size, and storage time of organ culture preservation. High risk criteria for corneal allograft failure were defined according to the presence of two or more quadrants of deep stromal vascularisation and/or previous immunologically mediated allograft failure(s).[8]

Out of the group of 248 patients a case (n = 21) and control group (n = 43) were selected. Cases were all transplant recipients undergoing a rejection episode, according to strict criteria described below (n = 23). Patients for whom it was not possible to differentiate between irreversible graft rejection and graft failure due to other causes were not included. Patients of whom no corneal tissue was available for DNA isolation (n = 2, one patient grafted for Fuchs' dystrophy and the other for HSK) were excluded. The control group was formed out of a group of patients with at least one year of follow-up after PKP and no episodes of graft rejection. This group was matched for age and sex. Patients with graft failure because of other causes than rejection were not excluded as long as their cornea could be evaluated for rejection during the study period. Eight out of 43 grafts failed irreversibly due to other causes than graft rejection, two grafts failed as a consequence of intractable glaucoma and six because of presumed slow endothelial decompensation.

In the group of cases, 12 out of 21 (57%) could be considered as high risk and in the group of controls 19 out of 43 (44%).

Patient, donor and graft characteristics of cases and controls are presented in Table 1. No significant differences were found between the two groups with respect to these characteristics. The indications for PKP are shown in Table 2.

Table 1. Clinical characteristics of recipients and donors from the case and control group

		Cases	Controls
Number		21	43
Age (years): mean (range)		57.2 (29-79)	51.6 (11-83)
Male:female ratio		1.0:1.1	1.0:1.0
Use of systemic immune suppression		1	1
History of ocular hypertension or POAG		6 (28.6%)	9 (20.9%)
History of HSK		7 (33.3%)	14 (32.6%)
Tear film insufficiency		2 (9,5%)	3 (7.0%)
Number of previous grafts:	0	15 (71.4%)	35(81.4%)
	1	4 (19.0%)	8 (18.6%)
	>1	2 (9.5%)	0 (0%)
Vascularisation of recipient cornea		11 (52.4%)	15(34.9%)
Additional procedures:	Cataract extraction	3 (14.3%)	9 (20.9%)
	Synechiolysis	3 (14.3%)	4 (9.3%)
	Iris reconstruction	1 (4.8%)	2 (4.7%)
Donor age (years): mean (range)		69.0 (20-89)	67.8 (16-86)
Donor sex; male:female ratio		1.7:1.0	1.9:1.0
Time in culture medium (days): mean (range)		15.8 (7-23)	15.9 (10-27)
Graft size (mm): mean (range)		7.5 (6.5-8.0)	7.5 (5.5-8.0)

Diagnosis of rejection

The time between PKP and the first rejection episode, not necessarily ending in graft failure was used to analyse graft outcome. The diagnosis of immune mediated allograft rejection was based on generally accepted criteria.[37] All corneal grafts had to become clear after surgery and a diagnosis of rejection was not made for at least ten days after surgery. Rejection episodes were not diagnosed during a period of elevated ocular pressure. The presence of a 'Khodadoust line' was considered a pathognomonic sign of graft rejection. In the absence of a Khodadoust rejection line, graft rejection was diagnosed by the presence of cells in the anterior chamber, in combination with an increase in (partial) corneal thickness and/or keratic precipitates limited to the graft. For patients with a history of HSK, graft rejection, and recurrence of herpes simplex virus (HSV) infection needed to be differentiated. If no Khodadoust line was observed, additional tests were needed to diagnose HSV infection. Aqueous humour was obtained by paracentesis of the anterior chamber to determine intra-ocular antibody production against HSV, expressed as the Goldmann-Witmer coefficient for HSV. Also, PCR analysis of HSV DNA was performed[38] to exclude an active ocular herpes

Table 2. Indications for penetrating keratoplasty (PKP) of cases and controls

Indication for PKP	Cases	Controls
HSK	7	12
Allograft failure	6	8
Keratoconus	-	11
Pseudophakic BKP	2	5
Corneal ulcers	4	3
Trauma	2	2
Fuchs' dystrophy	-	2

HSK, herpes simplex keratitis; BKP, bullous keratopathy

simplex infection. Herpes infected cases were excluded from analysis in this study.

Methods

Donor procurement and medical procedures did not change during the study period. All donor corneas were obtained from Bio Implant Service and the Dutch Eye Bank, Amsterdam, Netherlands. The donor corneas were organ culture preserved as described by Pels et al.[39] All donor corneas were stored in organ culture of Eagles minimum essential medium for at least seven days with a maximum of 27 days. PKP procedures were performed by one of three ophthalmic surgeons using similar surgical techniques. All patients were treated with a combination of prednisolone eye ointment (0.5%, at bedtime) and local dexamethasone/ gentamicin eye drops (0.1%, six times daily) after surgery, for 4 weeks. At least 1-1.5 years after PKP, dexamethasone eye drops were applied and gradually tapered off. If PKP was combined with a cataract extraction or removal of an intra ocular lens, additional eye drops were given, containing a non steroid anti inflammatory drug (0.1%, four times daily) during the first 3 months after surgery. Rejection reactions were treated with hourly application of prednisolone acetate 1% eye drops and three periocular injections with 0.1% dexamethasone, given every other day. Graft rejection has led to irreversible graft failure in nine out of 21 cases.

DNA typing for HLA

Corneal tissue was used for retrospective DNA HLA typing. For this purpose, corneal tissue of the recipients and corneal rims of donor corneas were collected at the time of surgery and stored frozen (at -80°C). After repeated transplantation blood samples containing peripheral blood mononuclear cells were taken from recipients to obtain DNA. Corneal tissues and blood-derived cell

suspensions were subjected to DNA extraction using the Qiagen DNA extraction kit (Boehringer, Mannheim, Germany) for blood and tissues, according to the manufacturer's instructions. DNA solutions were stored at -80°C until further amplification. The diagnosis of rejection at the end of the follow-up was made before the HLA typing was known. HLA typing was done without knowledge of graft outcome. This molecular typing of HLA-A, HLA-B and HLA-DRB1 (all low resolution) was performed according to a reverse hybridisation line probe assay as described by the manufacturer of InnoLiPa (Innogenetics, Gent, Belgium).[40]

Typing data were available in all 64 donor/recipient pairs for HLA-DR. For HLA-A and HLA-B one and five pairs were not available respectively, owing to shortness of donor DNA (n = 2), technical problems with PCR (n = 1) and problems with analysing the Lipa test results for HLA-B (n = 3). Analysis was performed both on the broad HLA typing level (A1, A2, A3, A9, A10, A11, A19, A28, B5, B7, B8, B12, B13, B14, B15, B16, B17, B18, B21, B22, B27, B35, B37, B40, B41, B42, B53, B70, DR1, DR2, DR3, DR4, DR5, DR6, DR7, DR8, DR9, DR10) and split typing level (splits from A9, A10, A19, A28, B5, B12, B16, B17, B21, B22, B70, DR2, DR3, DR5, DR6).

Analysis and statistics

Comparability of patient, donor and graft covariates between cases and controls were analysed using the χ^2-test for categorical variables and the independent T test for continuous covariates. To analyse rejection free graft survival, cases and controls were subdivided into a group with and a group without matched HLA subtypes. The group with matches consisted of cases and controls with one or two matches of HLA-A, HLA-B or HLA-DR. Unadjusted survival probabilities for the total group as well as the high and low risk group were estimated using Kaplan-Meyer statistics and differences were assessed using the log rank test.[41] All tests were two sided and a p value of less than 0.05 was taken as statistically significant.

To assess the clinical relevance of matching we used Cox regression analysis estimating the odds ratios (OR) and 95% confidence intervals for the association between HLA matching per HLA locus and duration of rejection free graft survival, adjusting for confounding variables. Covariates were chosen for inclusion in the model if they were mildly correlated ($p < 0.20$) with rejection according to univariate analysis. Using this selection criterion, only vascularisation of the recipient cornea was included in the model ($p = 0.12$).

RESULTS

The median follow up period of the control group (n = 43) was 2.6 years (range 1 - 4 years). The median time until rejection of the case group (n = 21) was 9 months (range 12 days to 1 year and 11 months).

The maximum amount of matches based on split typing for a patient in this study was three, which was detected in six controls and one case. The distribution of HLA-A, HLA-B and HLA-DR split matches in cases and controls is shown in Table 3. Recalculation of split HLA DNA typing results into broad typing results did not yield significant differences between cases and controls with regard to HLA-A and HLA-B matching. However, an increased amount of broad HLA-DR matches was found compared to the amount of split HLA-DR matches in four cases.

Corneal graft recipient-donor pairs with HLA-A matches had a longer rejection free graft survival compared with corneal grafts without HLA-A matches (log rank test, p = 0.034, Fig 1). We observed a trend towards a prolonged rejection free graft survival with increasing numbers of HLA-A matches. No difference was observed in rejection free graft survival time between cases and controls with respect to HLA-B matches (Fig 2) and HLA-DR matches (Fig 3).

Analysing rejection free graft survival for the high risk (n = 31) and low risk (n = 33) group separately, a stronger association between longer rejection free graft survival and HLA-A matching in the low risk group was found (log rank test, p = 0.013). Graft survival was not significantly longer with respect to HLA-B matches in the high or low risk group (data not shown). Analysis of the HLA-A

Table 3. Degree of HLA-A, HLA-B and HLA-DR matching of the case and control group

	No. of split matches	Cases	Controls
	0	16 *(76%)*	21 *(50%)*
HLA-A	1	4 *(19%)*	15 *(36%)*
	2	1 *(5%)*	6 *(14%)*
	0	14 *(74%)*	30 *(75%)*
HLA-B	1	5 *(26%)*	9 *(22,5%)*
	2	0	1 *(2,5%)*
	0	14 *(67%)*	25 *(58%)*
HLA-DR	1	6 *(29%)*	17 *(40%)*
	2	1 *(5%)*	1 *(2%)*

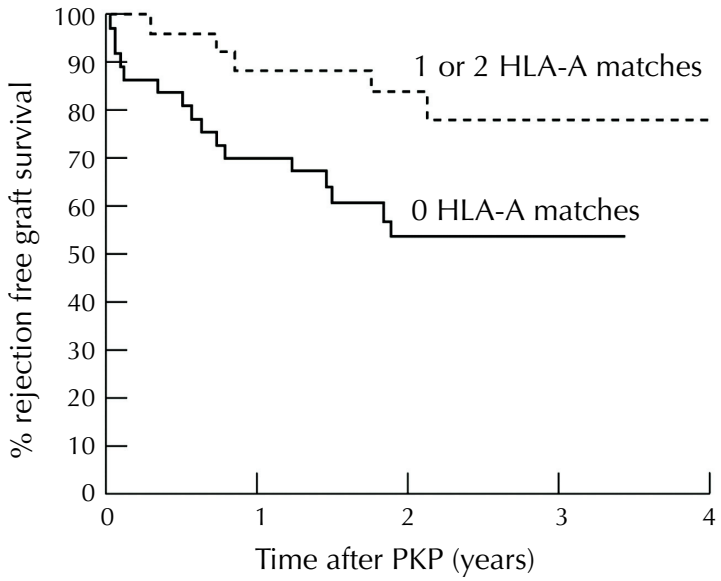

Figure 1. Kaplan Meyer curves indicating rejection free survival of corneal graft recipients with one or two matches at the HLA-A locus is significantly better than those with 0 HLA-A matches (log rank test, p = 0.030, n = 63).

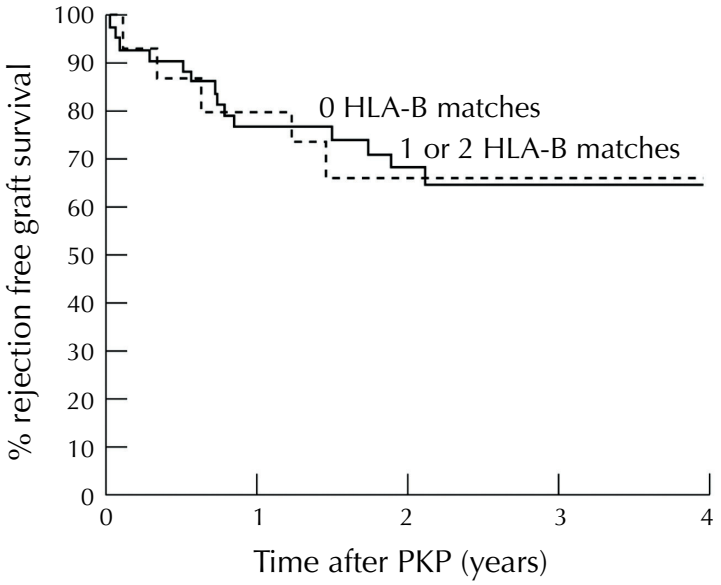

Figure 2. Kaplan-Meyer curves indicating the presence of HLA-B matches did not improve rejection free survival of corneal graft recipients (log rank test, p = 0.50, n = 59).

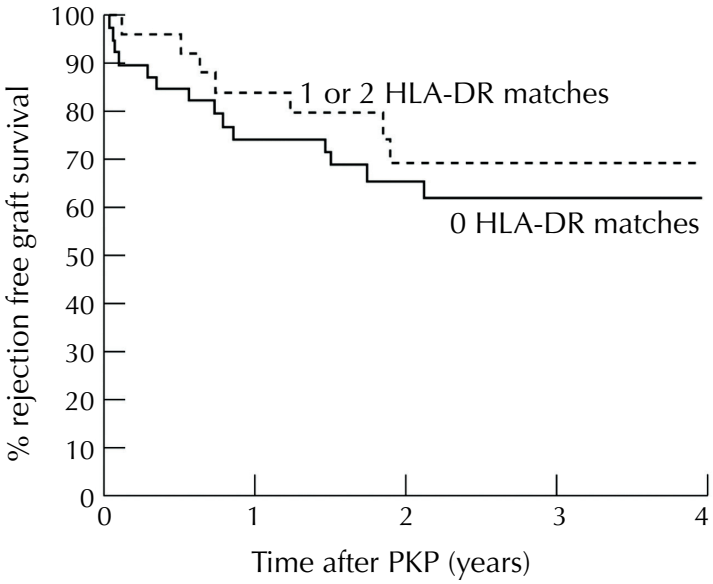

Figure 3. Kaplan-Meyer curves indicating the presence of HLA-DR matches did not improve rejection free survival of corneal graft recipients (log rank test, p = 0.92, n = 63).

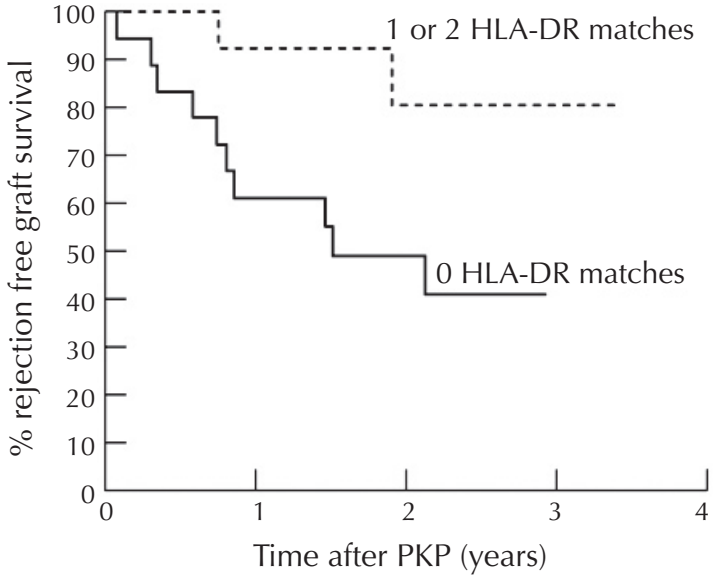

Figure 4. Kaplan-Meyer curves indicating HLA-DR matching in high-risk recipients showed a beneficial effect on the rejection free graft survival (log rank test, p = 0.030, n = 31).

Table 4. Odds ratios (OR) of corneal graft rejection

	OR[a] (95% Confidence Interval)
HLA-A unmatched transplants HLA-A matched transplants [b]	0.34 (0.13 – 0.95)
HLA-B unmatched transplants HLA-B matched transplants [c]	1.07 (0.38 – 2.97)
HLA-DR unmatched transplants HLA-DR matched transplants [d]	0.69 (0.27 – 1.70)

[a] Adjusted for vascularisation of the recipient cornea, [b] One or two matches for HLA-A, [c] One or two matches for HLA-B, [d] One or two matches for HLA-DR

and HLA-B matches together showed no effect in the total group or in the high risk group. However, we observed a beneficial effect of matching for HLA-DR in the high risk group (log rank test, p = 0.030, Fig 4).

According to Cox regression analysis, after adjustment for vascularisation of the recipient cornea, HLA-A matched transplants (one or two HLA-A matches) were almost three times less likely to reject than HLA-A unmatched transplants (Table 4). HLA-DR matched transplants were slightly, but not significantly, less likely to reject (Table 4).

DISCUSSION

The results showed that the presence of HLA-A matches was associated with prolonged rejection free graft survival. When considering patients at high risk for rejection, a beneficial effect of HLA-DR matches was shown. These HLA matches were found retrospectively in corneal graft recipients who received random donor corneas at the time of PKP.

Cases with and controls without an immune mediated graft rejection were analysed together according to their rejection free graft survival time. The first rejection episode, not necessarily leading to graft failure, was used as the end-point of analysis. From an immunological point of view it is more appropriate to use rejection free graft survival time rather than time to immunological graft failure. Whether a rejection episode will lead to graft failure is dependent on treatment protocols of a rejection reaction used in different transplantation centres. Furthermore, each rejection episode accelerates the postoperative loss of endothelial cells, resulting in earlier graft failure.[42,43]

A major advantage of HLA DNA typing, as used in this study, is that this method is less prone to errors than serological typing techniques.[31,32] Discrepancy rates of 10 - 25% have been reported for serological HLA-DR typing in kidney trans-

plantation.[29] DNA can be derived from any organic tissue, including corneal tissue, which is easily obtained at PKP[44] and nearly always available in contrast with blood samples necessary for serological typing.

The diagnosis of an immune mediated graft rejection is not always clearcut. Rejection and recurrence of HSK can be impossible to distinguish clinically and may coexist.[45] We excluded patients for whom it was not possible to differentiate between graft rejection and HSK.

Patient compliance is of great influence on graft survival.[6] In our study topical steroids were given for at least one year in all patients. All patients with graft rejection within 1 year were still using topical steroids. These data, however, are based on patient records and a contribution of patient compliance to graft rejection could not be fully excluded.

HLA-A and HLA-B antigens have been identified on corneal epithelium, stromal cells, and corneal endothelial cells.[19,46,47] The HLA class I antigens are targets for CD8+ cytotoxic T cells in the process of graft rejection.[21] Theoretically, matching for HLA-A and HLA-B therefore would reduce the amount of target antigens, which could lead to a decreased incidence of rejection. An accumulating number of authors suggested that HLA-A and HLA-B matching was associated with improved outcome of corneal graft survival in high risk recipients.[5,9-12,15,33,48,49] These data on HLA-A matching are in line with the results from our study. However, other studies, including the large Collaborative Corneal Transplantation Study, failed to demonstrate a correlation of HLA matches and graft survival.[16-18,50] A beneficial HLA-A matching effect was observed in all risk categories with a stronger association in low risk cases by Boisjoly et al.,[11] which is in accordance with our findings. In this study, HLA-B matches showed no significant effects on graft rejection. This might be due to the overall low number of matches observed in this study at the polymorphic HLA-B locus. In previous studies, matching of HLA-B showed a beneficial effect on corneal graft survival[5,10,12] and an adverse effect in others.[18,20]

Despite the fact that HLA-DR is considered to be important in renal transplantation,[29] the role of HLA-DR matching in corneal transplantation remains controversial.[49,51] Significant beneficial effects of HLA-DR matching in high risk recipients were reported using RFLP typing techniques,[26] but a historical control group was used. Japanese studies[33,34,44] using DNA typing techniques reported a strong beneficial effect of HLA-DP matching and no effect of matching for HLA-DR. This may be explained by the overall low number of HLA-DR matches reported by this group, using donors and recipients from different ethnic backgrounds. In our study, both donors and recipients originated mostly from the white population, and therefore from the same gene pool. This may add to the

explanation of the high number of coincidental HLA-A and HLA-DR matches we observed. In some studies, a beneficial influence of HLA-DR matching could not be found in low or high risk recipients,[16,17,52] whereas in other studies an adverse effect was reported.[28,51] However, in these studies serological typing techniques were used, which in general yield accurate broad but not split typing results. In our study HLA DNA typing included analysis of HLA split antigens. A beneficial effect of HLA-DR matching in high risk recipients was shown. After conversion of HLA-DR split to broad antigens (data not shown), a significant effect of matching could no longer be found, which is in line with the previously mentioned studies.

Expression of HLA-DR antigens carried on Langerhans cells has been demonstrated within normal corneal epithelium and stromal layers.[19,47] Migration and accumulation of Langerhans cells in the central part of the cornea, which is normally devoid of Langerhans cells[19,24] can be established by vascularisation and inflammation.[53] As a consequence of an increased number of Langerhans cells in the centre of the donor cornea, a rejection reaction may be provoked.[54] The beneficial effect of HLA-DR matching for high risk recipients as reported in our study might be explained by a higher number of Langerhans cells in the central area of the cornea after transplantation in this high risk group.

A drawback of this study is the overall low number of included patients. Owing to the random distribution of corneal grafts a relatively small amount of patients with more than one match at HLA-A, HLA-B or HLA-DR loci was included. As a consequence it was not possible to evaluate combinations of HLA-A and HLA-B matches or to evaluate the effect of HLA-DR in the absence of any HLA-A or HLA-B match.

Although the case and control group are comparable with respect to the characteristics mentioned in Table 1, the indication for transplantation were not completely comparable, with Fuchs' dystrophy (n = 2) and keratoconus (n = 11) being present only in the control group. One of the two excluded cases (no donor corneal tissue available) was transplanted for Fuchs' dystrophy; if this patient had been included, the only remaining difference would have been the indication of keratoconus. Analysis of rejection free graft survival without considering these 11 patients showed the same results for the high risk group (a longer rejection free graft survival for HLA-DR matched transplants). Furthermore, rejection free graft survival was longer for HLA-A matched transplants in the total group (n = 52), despite the loss of power (p = 0.047).

We included controls with at least 1 year of follow-up. However, rejections are still observed after 1 year. Therefore, further studies with a longer follow up time will be needed to show a beneficial long-term outcome with matching.

Organ culture preservation of donor corneas, as used for all donor corneas in this study, allows time to allocate corneas based on HLA matching. Prospective DNA HLA typing and transportation of donor corneas over long distances to the most suitable recipient could give logistical problems if short term preservation techniques, such as McCarey-Kaufman medium, are used. The cost-benefit ratio of providing matched corneal grafts should be investigated in more detail. Especially in more heterogeneous populations where less coincidental HLA matches are expected, allocation of matched donor corneas could be more difficult but also more effective in preventing corneal graft rejection.

In conclusion, molecular typing of HLA-A, HLA-B and HLA-DRB1 is an accurate method and offers the possibility to perform HLA typing at any time postoperatively, using corneal derived DNA. Although all corneal graft recipients received random donor corneas, retrospectively a significantly higher number of HLA-A matches was found, in favour of recipients with longer rejection free graft survival. Furthermore, a beneficial effect of matching for HLA-DR was shown for high risk recipients. These results add to the evidence that prospective molecular HLA-A and HLA-DR typing has a beneficial effect upon graft survival.

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CHAPTER 3

LONG-TERM OUTCOME IN HIGH-RISK CORNEAL TRANSPLANTATION AND THE INFLUENCE OF HLA-A AND HLA-B MATCHING

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ABSTRACT

Purpose: To evaluate long-term follow-up of high-risk corneal transplants allocated after matching for broad HLA-A and HLA-B antigens and to establish whether matching for HLA-A and -B antigen "splits" would result in a reduced risk of immunologic graft failure.

Methods: A total of 303 high-risk corneal transplants was included. Class I antigen-matched donor corneas were obtained using broad HLA-A and -B antigen data and accepting 0 or 1 mismatch at each locus. Analysis of HLA antigens was performed also on the split typing level. The influence on immunologic graft failure for an increasing number of matched class I antigens based on split typing was analyzed with Kaplan–Meier statistics and Cox regression. Graft survival and indication for transplantation were investigated.

Results: Rejection was the cause of 34% of all graft failures. A significantly higher immune failure free graft survival was found in a group with 0 or 1 HLA-A and -B mismatch based on split typing (log rank test, $p = 0.002$). A beneficial effect of matching for split antigens was shown with multivariate analysis (odds ratio, 0.41).

Conclusions: One third of graft failures in our high-risk population was caused by irreversible graft rejection. Allocation of donor corneas based on a 0 or 1 split antigen mismatch at both HLA-A and -B loci could contribute to a higher immune failure free graft survival and could result in a higher overall graft survival.

INTRODUCTION

Allograft rejection is reported to be the leading cause of corneal transplant failure.[1,2] Patients having corneal vascularization are considered to be high risk of allograft rejection and failure as are individuals with a history of graft failure.[3-6] Current research has identified HLA-A and -B antigens on corneal epithelium, stromal cells and corneal endothelial cells.[7-9] These HLA class I antigens have been shown to be targets for cytotoxic T cells in the process of graft rejection.[10] It might be expected that, as with other solid organ transplantation, HLA-A and -B matching would reduce the amount of target antigens, which could then lead to a decreased incidence of graft rejection. Although many studies have reported a beneficial effect of HLA-A and -B matching for corneal graft survival in high risk patients, no consensus about HLA class I matching has yet been reached.[11] Theoretically, a decreasing amount of mismatched class I antigens would decrease the risk of allograft failure. However, allocating donor corneas based on a 0 class I mismatch will substantially increase waiting time and the cost of corneal transplantations. Consequently, it is essential to know whether an increasing amount of matches significantly reduces the incidence of graft failure. With the currently available techniques, it is possible to perform HLA-A and -B typing on "split" level (subtypes of broad specification). Allocation of donor corneas based on the so-called "split-typing" level have to be shown to be beneficial, as more logistical efforts should be made to use this type of allocation. The current practice at the Eye Hospital Rotterdam is to use HLA-A and -B matched donor corneas based on a broad typing level for high-risk patients. This retrospective study was performed to evaluate the long-term graft survival of high-risk HLA-A and -B matched corneal grafts and to analyze whether allocation on the split-typing level contributes in a decreased risk of immunologic graft failure.

PATIENTS AND METHODS

Patients

Between January 1982 and January 1996, 2471 penetrating keratoplasties (PKPs) were performed at the Eye Hospital Rotterdam. HLA-A and -B matched donor corneas were obtained for patients considered to be at high-risk (n = 323, 13.1%) due to either previous rejected transplants or deep stromal vascularization in two or more corneal quadrants. Clinical records of all high-risk patients who received a matched corneal transplant were reviewed for age, gender, a

history of glaucoma or herpes simplex keratitis (HSK), number of previous grafts and previous matched grafts, current and primary indication for transplantation, and the final outcome of the corneal graft. All corneal grafts had to become clear after surgery, and a diagnosis of immunologic graft failure could not be made within a 14-day period after transplantation. The diagnosis of immunologic graft failure was made by one of the cornea surgeons of the Eye Hospital Rotterdam. Grafts were declared as immunologically failed if the following signs did not clear under treatment within 2 months: keratic precipitates limited to the graft and a Khodadoust rejection line and/or increase in (partial) corneal thickness due to edema in combination with a slight to moderate cellular response in the anterior chamber. Information about graft size and donor age was collected. We based our classification of 14 possible indications for corneal transplantation on the classification of the Kok-Van Alphen corneal study group. Possible indications were anterior and stromal dystrophies, congenital malformation, keratoconus, buphthalmus, scrophulosis (interstitial keratitis as part of lymphoglandular tuberculosis), leucoma or ulcer, HSK, melting diseases, Fuch's dystrophy, (pseudophakic) bullous keratopathy (PBK), trauma, chemical or thermal burns, allograft failure, and a category of "other" indications. For statistical purposes, only indications reported more than seven times were included in the analysis to evaluate this variable as a risk factor for immunologic graft failure.

We excluded patients who were lost to follow-up within the first 2 postoperative weeks (n = 15; two patients died within two weeks after transplantation and 13 patients were followed by ophthalmologists in other hospitals). Patients whose transplants never became clear after PKP (n = 5, four primary failures and one expulsive hemorrhage) were also excluded. A total of 303 high-risk and HLA-A and -B matched corneal transplants met the inclusion criteria and were included in this study.

Methods

HLA-A and HLA-B typing of donors and recipients was performed using the complement-dependent cytotoxicity assay at the Department of Immunohematology and Blood Transfusion at the Leiden University Medical Center, accredited by the European Federation for Immunogenetics.[12] Analysis was performed both on the broad HLA typing level (A1, A2, A3, A9, A10, A11, A19, A28, A36, B5, B7, B8, B12, B13, B14, B15, B16, B18, B21, B22, B27, B35, B37, B40, B41, B42, B46, B47, B48, B53, B59, B67, B70 and B73) and split-typing level (splits from A9, A10, A19, A28, B5, B12, B15, B16, B17, B21, B22, B40 and B70). Donor corneas were allocated based on broad typing in which more than two mismatches were not accepted. All donor corneas were obtained from Bio

Implant Service (tissue branch of The Netherlands Transplant Foundation) and the Dutch Eye Bank, The Netherlands. Patients were followed by the cornea surgeons at the Eye Hospital Rotterdam in a regular pattern: 1 week, 4 weeks, 8 weeks, 3 months, 6 months, 9 months, 12 months, 18 months, 2 years, 2.5 years, 3 years, and annually thereafter. All patients were treated with topical dexamethasone eyedrops (0.1%, six times daily) and chloramphenicol (0.5%, three times daily) for 2 months after transplantation. Dexamethasone eyedrops were gradually tapered off within a minimum of 1 year after transplantation. Donor procurement and medical procedures did not change throughout the duration of the study.

Statistics

Subgroups of patients were made based on the number of HLA-A and -B mismatches at split-typing level. The good match group was formed by patients with no or one mismatch (n = 216). The moderate match group was formed by patients with two or more mismatches (n = 87). Comparability of patient, donor, and graft covariates between the subgroups were analyzed using the χ^2 test and the independent t test.

Event-free survival (EFS) and overall survival (OS) were calculated using Kaplan-Meier statistics, and data of the subgroups were compared with the logrank test. EFS is defined as transplantation to immunologic graft failure. Patients with graft failure because of causes other than rejection were censored at the time of their graft failure. OS is defined from transplantation until graft failure from any cause. Patients who did not experience (immunologic) graft failure were censored at the time of their last follow-up. Odds ratio (OR) and 95% confidence interval (CI) and adjusted survival probabilities for the different subgroups were estimated with the Cox proportional hazards model. Variables moderately correlated with graft failure according to univariate analyses ($p < 0.20$) were included in the model.

RESULTS

The median follow-up period for the 303 high-risk corneal transplants was 4.2 years. Eighty-seven percent of corneal grafts survived 1 year after transplantation, 71% survived 3 years and 59% survived 5 years. During the entire follow-up period 56.5% of all corneal grafts remained functional and clear. Immune rejection was the cause of 34.1% of all graft failures (45 grafts). Other causes of failure were slow endothelial decompensation (27 grafts), vascularized corneal

Table 1. Patient, donor, and graft characteristics of the total study population and subgroups based on split matching

		Subgroup based on split matching	
	Study Group	Good match group	Moderate match group
Number	303	216	87
Age (yr), mean (range)	55.8 (6.2 – 86.9)	56.5 (6.6 – 84.6)	54.0 (6.2 – 86.9)
Male: female ratio	1.0: 0.67	1.0: 0.76	1.0: 0.45
History of glaukoma (%)	18.2%	17.9%	18.7%
History of HSK (%)	95 (31,4%)	59 (27.3%)	36 (41.4%)
No. of previous matched transplants (mean)	1.16	1.13	1.21
No. of previous transplants (mean)	2.28	2.28	2.25
Graft size (mm), mean	7.62	7.62	7.63

HSK, herpes simplex keratitis

ulcer or perforation in 19 grafts, of which seven were a consequence of herpetic keratitis, corneal edema secondary to glaucoma (seven grafts), PBK (five grafts), phtisis bulbi (four grafts), and sequelae of trauma (two grafts).

Patient, donor, and graft characteristics of the total study population and subgroups are presented in Table 1. A history of HSK was the only variable with a significant difference between the two subgroups (p = 0.02). A history of HSK,

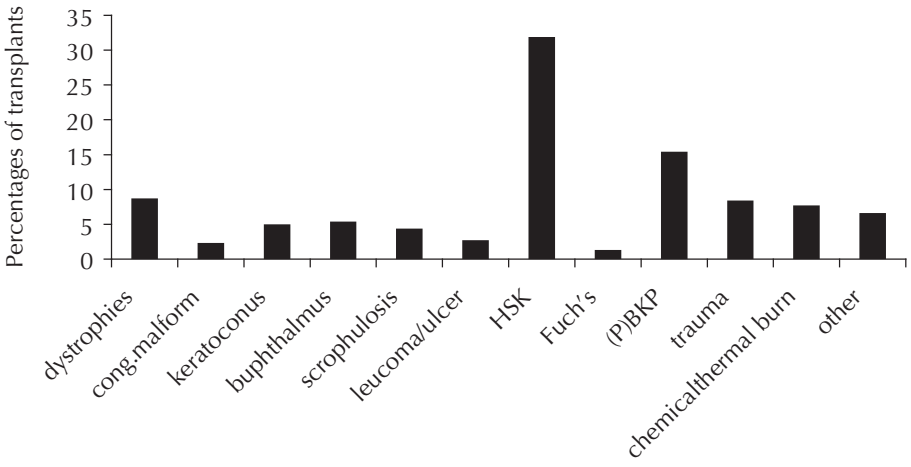
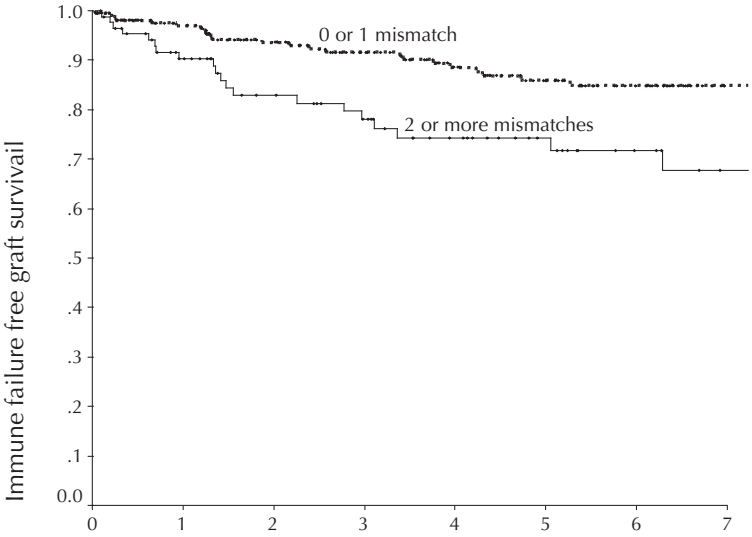


Figure 1. Indications for the primary transplantation.



Patients in FU (0 or 1 mismatch)	216	179	130	87	47
Cum events		6	15	22	23
Cum failures		24	52	70	78
Cum LTFU		12	25	37	
Patients in FU (≥2 mismatches)	87	68	46	28	15
Cum events		8	16	19	20
Cum failures		13	28	37	40
Cum LTFU		4	10	12	

Figure 2. Kaplan-Meier curves indicate a longer immune failure-free graft survival for corneal transplants of the good match group with zero or one mismatch based on split typing (log-rank test, p = 0.002).

however, was not correlated with immune failure in univariate analysis. Percentages of the primary indications for transplantation in these patients undergoning high-risk corneal transplantation because of repeated corneal transplantation or stromal vascularization are presented in Figure 1.

We investigated the relationship of HLA mismatching and immunologic graft failure for split typing. Considering long-term graft survival, a significantly longer immune failure-free graft survival was found in the good match group (log-rank test, p = 0.002, Fig. 2). Comparing groups with either zero, one, two, three or four

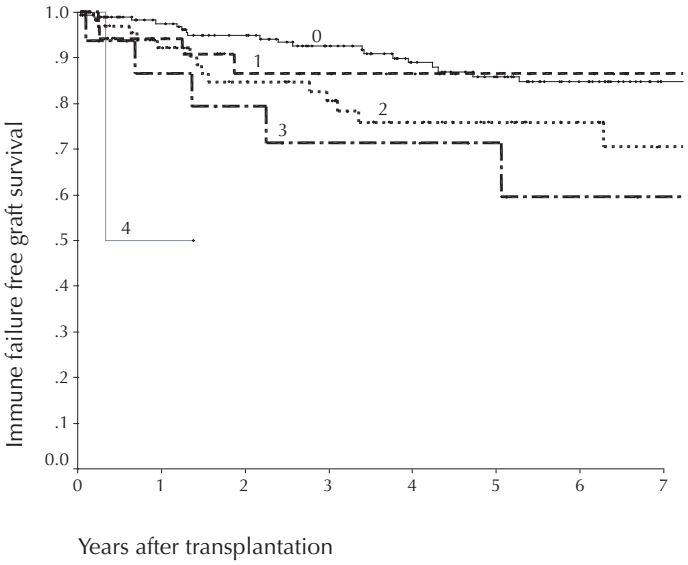


Figure 3. Kaplan-Meier curves indicate a tendency for more mismatches associated with more immune failure (log-rank test, p = 0.001).

split antigen mismatches, a tendency for more mismatches associated with more immune failure was seen (log-rank test, p=0.001, Fig 3). Besides matching, other factors could have influenced immunologic graft failure. To correct for these possible confounding variables, we performed a multivariate analysis adjusting for variables moderately correlated with immune failure. Only the variables of "indication for transplantation" and "number of previous grafts in the same eye" were correlated (p = 0.03 and 0.001, respectively). After multivariate analyses with Cox regression methods, we noted that a significant beneficial effect of fewer split antigen mismatches could still be found (OR = 0.41, with 95% CI 0.23-0.73).

The effects of HLA-A and HLA-B split mismatches on immune failure-free graft survival were analyzed individually. According to this analysis using Cox regression, zero mismatches at either one of these loci was significantly associated with a longer immune failure-free graft survival. The benefits of HLA-A were more pronounced (p = 0.008 for HLA-A and p = 0.025 for HLA-B).

To evaluate the impact of class I mismatches based on split typing on overall graft survival, we performed Kaplan-Meier statistics and multivariate Cox regression with graft failure as the event. As expected, having zero or one mismatch was less correlated with overall graft failure than with immune failure; nevertheless, a significant beneficial effect of fewer split antigen mismatches could still be found (log-rank test, p = 0.04, Fig 4, OR = 0.66, with 95% CI 0.45-0.96).

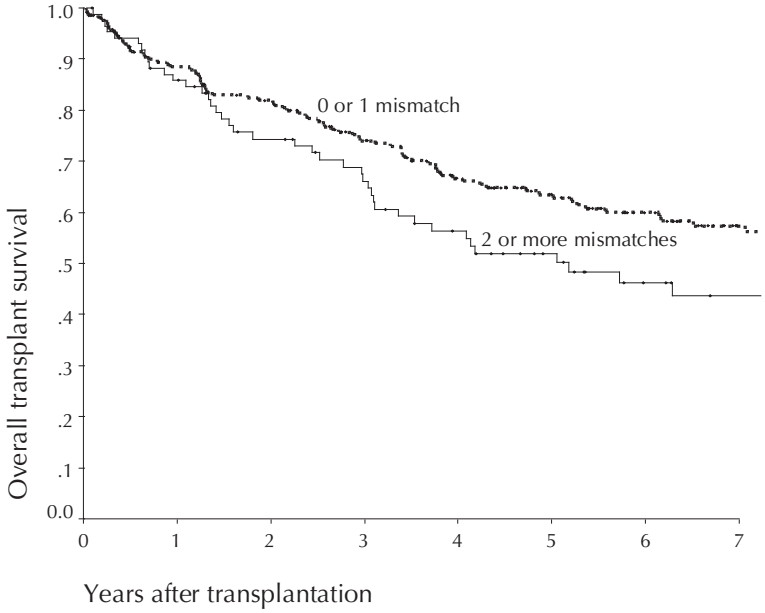


Figure 4. Kaplan-Meier curves indicate a longer overall survival for corneal transplants of the good match group with zero or one mismatch based on split typing (log-rank test, p = 0.04).

DISCUSSION

The results of this study show the advantages of matching HLA-A and HLA-B antigens using split typing for high-risk corneal transplantations. Grafts with up to one mismatch on a split typing level had a significantly longer immune failure-free survival compared with grafts with two or more mismatches.

Many studies suggest that HLA-A and HLA-B matching is associated with an improved outcome of corneal graft survival in high-risk corneal transplantations.[3,13-20] Other studies, such as the large Collaborative Corneal Transplantation Study (CCTS), failed to demonstrate a correlation of HLA matches and graft survival.[11] Most reports do not describe whether broad antigens or antigen splits were used in the mismatch calculation. Current practice, when using matched donor corneas, allocates donor corneas based on broad typing.[21] Consequently, it is most likely that the majority of studies describes the influence of HLA broad matches on corneal graft survival. In this investigation, however, we analyzed the influence of HLA matching on immunologic graft failure on a split-typing level, showing a valuable effect when split antigens were used in the mismatch calculation. Analogous to this finding, a previous study showed that HLA-DR

matching was beneficial for high-risk corneal transplantations only when split antigen typing results were used.[22]

Studies differ in their definition of high-risk, thus making it difficult to compare graft survival rates. In our study, patients were considered to be at high risk of corneal transplantation failure if they had deep stromal vascularization in two or more quadrants or if they had a previous corneal graft failure due to rejection in the same eye. The CCTS included high-risk patients according to equal criteria, making it comparable with our own investigation. The overall failure rate reported by this group, using an intensive postoperative topical immunosuppressive regimen was 35% at 3 years postoperatively. These findings are comparable with our result of 39% graft failure at 3 years. Our survival rates compare favorably with other studies, despite the inclusion of all risk categories in these studies.[23]

One third of graft failures in our study were due to an irreversible rejection reaction. Previous investigations reported similar results, showing that allograft rejection is still the leading cause of corneal graft failure.[23,24] Overall graft survival depends also on the presence of nonimmunologic factors causing graft failure, such as improvement of surgical techniques,[25,26] training of corneal surgeons,[27] and the use of newer topical or systemic immunosuppresive medication.[28-30] Attributing the cause of graft failure to rejection-related reasons or other nonrejection-related reasons can be difficult. In particular, rejection and recurrence of HSK can be impossible to distinguish clinically, more so during our investigation as this differentiation had to be made retrospectively. Even if graft failure due to any cause was taken as an event in the survival analysis, a beneficial result for the good match group based on split typing was shown.

Although this study was performed retrospectively, we were not aware of the number of HLA matches at the time of diagnosing the final graft outcome because these data were kept in a separate data file. The good and moderate match subgroups were comparable with respect to most characteristics. However, a higher percentage of patients with a history of HSK were included in the moderate match group. Analysis of immune failure-free graft survival without considering all HSK patients showed equal results.

In conclusion, one third of all graft failures of our investigated high-risk corneal transplantations were due to an irreversible graft rejection. This number could possibly be lowered by allocating donor corneas based on split antigen matching since fewer HLA-A and HLA-B mismatches on the split antigen level contribute to a higher immune failure-free graft survival and to a higher overall graft survival.

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CHAPTER 4

COMPARISON OF COMPLICATION RATES AND POSTOPERATIVE ASTIGMATISM BETWEEN NYLON AND MERSILENE SUTURES FOR CORNEAL TRANSPLANTS IN PATIENTS WITH FUCHS' ENDOTHELIAL DYSTROPHY

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Submitted

ABSTRACT

Purpose: Evaluation of corneal astigmatism and suture related complications for transplants sutured with Nylon and transplants sutured with Mersilene in primary corneal transplants for Fuchs' endothelial dystrophy.

Methods: Retrospective observational and comparative study between transplants sutured with either Nylon 10/0 or 11/0 (n = 108) or Mersilene 11/0 (n = 58). Hundred and sixty-six eyes of 140 patients who received a primary penetrating keratoplasty for Fuchs' endothelial dystrophy between 1995 and 2001 at the Rotterdam Eye Hospital, Netherlands were included.

Results: Overall transplant survival did not differ between groups (log rank test, p = 0.24). A significant lower astigmatism was seen in transplants sutured with Nylon during the first two years after transplantation (p = 0.03). Transplants sutured with Mersilene had a significantly higher risk of surgical intervention to correct astigmatism or wound dehiscence after transplantation (Hazard Ratio 2.83 with 95% Confidence Interval 1.34-6.01). Time to first infiltrate, metaplasia or cheesewiring was significantly less in the Mersilene group (p < 0.01). There was a tendency towards a higher risk of complications associated with loose or broken sutures in the Nylon group (Hazard Ratio 2.00 with 95% Confidence Interval 0.57-6.98), which was more pronounced after two years.

Conclusion: Mersilene sutures are less accurate in the early postoperative period compared to Nylon sutures with regard to astigmatism and risk of developing complications. In long-term follow-up, the long lasting tensile strength of polyester may lead to fewer complications associated with loose or broken sutures for transplants sutured with Mersilene. These favorable long-term effects of Mersilene sutures may outweigh its short-term disadvantage in patients with Fuchs' endothelial dystrophy.

INTRODUCTION

The most established treatment for Fuchs' endothelial dystrophy is penetrating keratoplasty.[1] Graft survival for Fuchs' dystrophy is good, with long-term graft survival rates of 89%.[2,3] One of the major complications impairing visual acuity after successful penetrating keratoplasty is high astigmatism.[2] Many factors can influence postoperative astigmatism, such as malpositioning of donor and recipient corneas, trephination irregularities, uneven tension on sutures and suturing technique. Selective removal of individual interrupted sutures has been proven to be effective in the reduction of astigmatism after penetrating keratoplasty.[4-7] When acceptable astigmatism is achieved, the remaining sutures are generally left in place. However, the commonly used suture material of Nylon biodegrades over time and can weaken or loosen. Loose sutures are associated with complications such as (sterile) infiltrates, microbial keratitis, endophthalmitis and allograft rejection.[8-10] Furthermore, wound dehiscence and large changes in astigmatism can occur after suture removal or suture degradation.[11-13] It would be attractive to use a suture material which can be left in place permanently without loosing tensile strength. Patients with Fuchs' endothelial dystrophy are at elevated risk of wound dehiscence after penetrating keratoplasty.[8] Wound dehiscence has been related to age, preoperative corneal edema, use of Nylon sutures (by not inducing inflammation) and the use of postoperative corticosteroids.[8,14,15] Consequently, Fuchs' patients may benefit from a non-absorbable suture. A non-absorbable suture material which is sometimes used is Mersilene, a polyester monofilament which is neither hydrolyzed nor degraded by ultraviolet light.[16] Theoretically, Mersilene is more suitable than biodegradable sutures to control long-term postoperative astigmatism and to prevent wound dehiscence as it can be left in place permanently.

In this study, we compare mid-term stability of the corneal surface and suture related complications in primary corneal transplants for Fuchs' endothelial dystrophy sutured with either Nylon or Mersilene filaments.

MATERIALS AND METHODS

A retrospective and observational study was done on 166 consecutive penetrating keratoplasties performed at the Rotterdam Eye Hospital, Netherlands between 1995 and 2001. Only primary not HLA-matched transplants performed in patients with Fuchs' endothelial dystrophy were included. Transplants were sutured with either Nylon or Mersilene sutures. Transplants in which combina-

tions of both materials were used and patients who did not receive follow-up examinations at the Rotterdam Eye Hospital were excluded. Preoperative, intraoperative and postoperative data were collected retrospectively from patient charts and from the national follow-up program on keratoplasties. Preoperative data included patient age, gender, involved eye, history of glaucoma, previous eye operations, best corrected visual acuity (BCVA) and preexistence of systemic disease such as diabetes mellitus or collagenous disease. The diameter of the donor graft was systematically 0.50 mm larger than that of the recipient. Trephination of the donor button was done from the endothelial side by means of a disposable punch (Medical Workshop, Groningen, the Netherlands). Trephination of the recipient cornea was done by a Hesburg Barron suction trephine. All penetrating keratoplasties were performed by corneal surgeons at the Rotterdam Eye Hospital. Suturing techniques depended on the preference of the surgeon: one running suture (Nylon 11-0 or Mersilene 11-0), 16 interrupted sutures (Nylon 10-0 or Mersilene 11-0) or a combination of 8 interrupted sutures with one running suture. Intraoperative keratoscopy was used to adjust suture tension whereafter, all knots were buried in the recipient cornea. Patients received subconjunctival antibiotics and Dexamethasone phosphate at the end of the procedure. All patients were treated with a fixed combination of topical Dexamethosone eye drops (0.1%, six times daily) and Chloramphenicol (0.5%, three times daily) for at least two weeks after transplantation. Dexamethason eye drops were gradually tapered off to one drop daily within one year after transplantation. Additional procedures performed (such as cataract extraction with intraocular lens implantation or intraocular lens exchange), intraoperative complications, suture material, suturing technique and graft size were noted. Postoperatively, transplant survival, rejection episodes, intra ocular pressure (IOP), suture related procedures and suture related complications such as neovascularization, infiltration, loose or broken sutures, epithelial defects, metaplasia, filaments, wound dehiscence and cheesewiring were noted. Transplant survival was defined as the time that a transplant was functionally clear. Neovascularization was defined as deep vascular growth in the donor at one or more suture sites. Infiltration was defined as deep infiltrates at the suture site. Postoperatively, patients were followed by the cornea surgeons in a regular pattern at 1 week, 4 weeks, 8 weeks, 3 months, 6 months, 9 months, 12 months, 18 months, 2 years and annually thereafter. BCVA and keratometry were noted at 3 months, 6 months, and yearly thereafter. Astigmatism was measured with a calibrated Javal keratometer. Interrupted sutures were removed selectively to reduce astigmatism one by one in cases with more than four diopters of astigmatism. Except for

broken sutures, which were removed immediately at time of presentation. There was no set protocol for final suture removal.

Statistics

Subgroups of transplants were based on suture type. The Nylon subgroup consisted of 108 transplants of 95 patients and the Mersilene subgroup consisted of 58 transplants of 53 patients. Eight patients received a transplant sutured with Nylon in one eye and Mersilene in the other eye. Comparability of preoperative characteristics between suture type groups were analyzed using the χ^2 test for categorical variables and the Students t test for continuous covariates.

Eyes with astigmatism equal to or greater than 4.00 D were considered highly astigmatic. Postoperative keratometric astigmatism (diopters) in the first two years as it differed between the two suture materials, was adjusted for possible confounding factors and was analyzed with mixed model ANOVA using SAS software 8.2. Before analysis, keratometric astigmatism was converted from the polar values (cylinder and axis) to Cartesian coordinates (X and Y), according to Holladay.[17] Possible confounding variables included in the model were suturing technique, age and patients having two eyes operated. The covariance structure of the repeated measurements was assumed to be random with the variance components between patients and within patients (between both eyes, between follow-up times and residual error). The modification of the suture material-effect on astigmatism through time was also tested. The mean absolute change in astigmatism between the different follow-up times was analyzed with vector analysis and also compared between the two groups with mixed-model ANOVA. The dependent variable in this model was the Ln-transformed vectorial change in keratometric astigmatism between two follow-up times. As independent variables along with Nylon or Mersilene sutures, left or right eye, suture technique and age were included. No structure was imposed on the (co)variance of repeated measurements.

Overall graft survival was calculated using Kaplan Meier statistics and data for the subgroups were compared with the log rank test.

Only the first transplant of a patient was included for complication analysis. If one patient had a transplant sutured with Nylon and another with Mersilene, both transplants were included. Each suture related complication was scored as a different event. If a complication occurred more than once, only the first was scored as an event. Transplants, which were not complicated by an event were censored at the time of last follow-up. Event-free survivals for each complication were estimated with the Cox proportional hazards model. Possible confounding factors such as suturing technique and age were included in the model to es-

timate adjusted survival probabilities. Besides an individual evaluation of each complication, the more serious complications such as endophthalmitis, neovascularization, infiltration and wound dehiscence were categorized in one group and the effect of suture type on this category was also evaluated. Complications related to loose or broken sutures were also categorized in one group for the evaluation of suture effect on this category. All broken or loose sutures leading to corneal infiltration, endophthalmitis, wound dehiscence, rejection reaction (reversible and irreversible) or progression of astigmatism of 3 or more diopters were considered as events in the category of complications related to loose or broken sutures.

Some complications can occur more than once without interfering with transplant survival. For this reason, the yearly complication rate for certain complications was also calculated using Poisson regression analysis. All transplants were included in this analysis. A general linear model was used with maximal 2 repeated measurements (left or right eye) per patient. Empirical standard errors of the estimated coefficients (denoting the natural logarithm of the complication rate ratio) were estimated using the GEE method.[18] A level of significance of $p = 0.05$ was used.

RESULTS

Preoperative patient data did not reveal significant differences between the Mersilene or Nylon suture groups (Table 1). However, there was a significant difference among groups in distribution of suturing technique ($p < 0.01$, Table 2). Penetrating keratoplasty was combined with cataract extraction and intraocular lens implantation in 66 eyes (61%) of the Nylon suture group in 29 eyes (50%) of the Mersilene suture group. The overall low intraoperative complication rate did not differ between suture groups ($p = 0.85$). The most encountered intraoperative complication, capsular rupture with or without vitreous loss, occurred in 9 eyes (8.3%) of the Nylon group and in 4 eyes (6.9%) of the Mersilene group. The average follow-up between the two groups was significantly different, 4.13 ± 1.54 (SD) years for the Nylon group (median 4.04 years) and 3.15 ± 1.88 years for the Mersilene group (median 2.55 years). Overall transplant survival was not significantly different between the two groups (log rank test, $p = 0.24$, Figure 1). Thirty-three (21.6%) of 153 eyes without a history of glaucoma developed an IOP more than 21 mmHg during the first postoperative year. In most cases, this IOP rise was related to the use of topical corticosteroids. Response to IOP

Table 1. Preoperative patient data

	Mersilene (n = 53)	Nylon (n = 95)	p-values
Gender	64% Female	66% Female	0.80
Age (mean, yrs)	72.8	70.5	0.10
Pseudophakia	39%	27%	0.15
History of glaucoma	7%	8%	0.74
Diabetes Mellitus	9%	10%	0.82
Collagenous disease	7%	9%	0.61

Table 2. Distribution of suturing techniques

	Mersilene (58 eyes)	Nylon (108 eyes)
Interrupted sutures	18 (31.0%)	12 (11.1%)
Running suture	4 (6.9%)	1 (0.9%)
Combination of one running suture with interrupted sutures	36 (62.1%)	95 (88.0%)

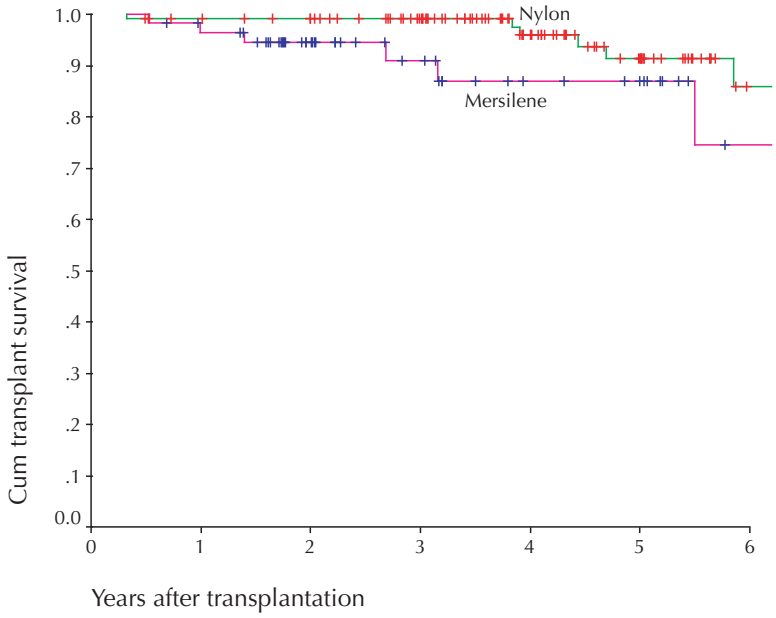

Figure 1. Overall transplant survival for suture type, log rank test, p = 0.24.

lowering medication was good in all cases. Suture material was not found to be related to IOP rise.

Table 3. Average and standard deviation of pre and postoperative visual acuity and postoperative astigmatism

	Preoperative		3 months		6 months	
	Mersilene (n = 58)	Nylon (n = 108)	Mersilene (n = 56)	Nylon (n = 107)	Mersilene (n = 56)	Nylon (n = 106)
BCVA	0.24 ± 0.14	0.24 ± 0.17	0.31 ± 0.21	0.32 ± 0.18	0.42 ± 0.24	0.46 ± 0.23
Flat k-readings	-	-	40.9 ± 3.7	42.0 ± 2.8	42.2 ± 3.0	42.8 ± 3.2
k-cylinders	-	-	5.63 ± 3.15	5.17 ± 2.92	5.24 ± 3.22	4.38 ± 2.60
% ≥ 4 D astigmatism	-	-	63.0%	50.5%	52.7%	44.7%

BCVA, best corrected visual acuity; n = number of eyes

Visual acuity and astigmatism

Mean preoperative BCVA was 0.24 ± 0.14 in both groups. Further pre and postoperative values are summarized in Table 3. No significant difference in BCVA was seen among the groups at all follow-up periods. The keratometric cylinders are presented graphically in Figure 2. High astigmatism (≥ 4 D) did not occur more frequently in either group at any follow-up period. A mean 0.88 ± 0.41 D lower astigmatism was seen in the Nylon group the first two years after transplantation (mixed model ANOVA, p = 0.03). At three years follow-up a slightly lower astigmatism was observed in the Mersilene group. There was no significant difference between groups in astigmatic change between follow-up periods (Table 4).

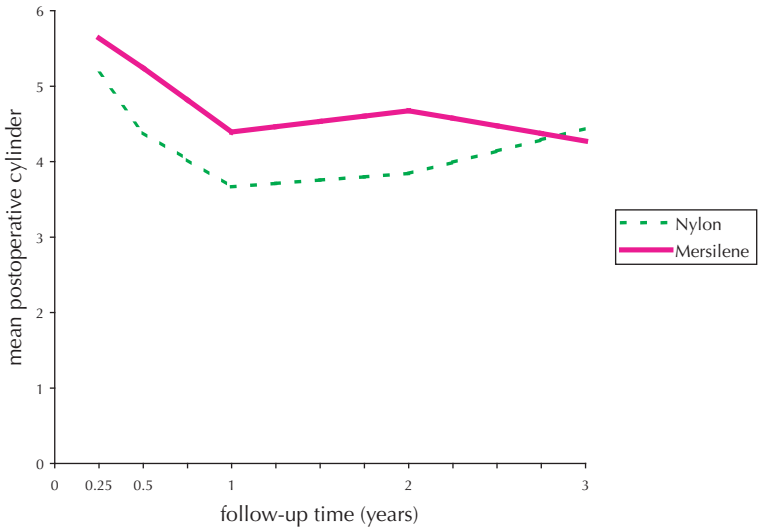

Figure 2. Mean keratometric cylinder at follow-up periods for suture type.

1 year		2 years		3 years	
Mersilene (n = 52)	Nylon (n = 104)	Mersilene (n = 36)	Nylon (n = 100)	Mersilene (n = 25)	Nylon (n = 86)
0.52 ± 0.27	0.57 ± 0.25	0.58 ± 0.27	0.58 ± 0.24	0.54 ± 0.28	0.56 ± 0.26
43.0 ± 3.7	43.5 ± 3.2	42.8 ± 3.5	44.0 ± 2.8	42.9 ± 3.7	44.2 ± 2.7
4.39 ± 2.83	3.67 ± 3.15	4.67 ± 2.89	3.84 ± 2.96	4.27 ± 2.63	4.44 ± 3.09
41.2%	28.9%	34.9%	34.4%	43.5%	41.9%

Suture adjustment

Significantly more eyes in the Mersilene group required surgical changing of suture tension by the addition or the replacement of sutures due to corneal astigmatism, according to multivariate analysis with Cox regression methods (Hazard Ratio (HR) = 2.83 with 95%Confidence Interval (CI) 1.34-6.01). The frequency of suture adjustment by selective suture removal in the steep axis was not significantly different between groups (Cox analysis, HR = 0.84, with 95% CI 0.52-1.37). All transplants with single running Mersilene sutures (n = 4) needed surgical correction shortly after transplantation. The running sutures were too loose in two cases, plus cheesewiring caused loosening of the sutures in one eye and the transplant was too flat in another.

Suture-related complications

Time to first infiltrate, metaplasia or cheesewiring was significantly shorter in the Mersilene group (Cox regression analysis, $p < 0.01$).

Table 4. Comparison of absolute cylindric change according to vector analysis at different follow-up periods between the Mersilene and Nylon groups

Follow-up period	Mersilene mean astigmatism (D)	Nylon mean astigmatism (D)	Adjusted effect of Mersilene relatively to Nylon*		
			Exponent β	95% Confidence Interval	p -value
3 to 6 months	4.3	3.2	1.22	0.98-1.53	0.08
6 months to 1 year	3.7	3.4	1.05	0.81-1.37	0.71
1 to 2 years	4.4	3.9	1.30	0.98- 1.72	0.07
2 to 3 years	3.0	4.6	0.80	0.54-1.19	0.27

*Adjusted for the possible inclusion of two transplants per patient, suture technique and age

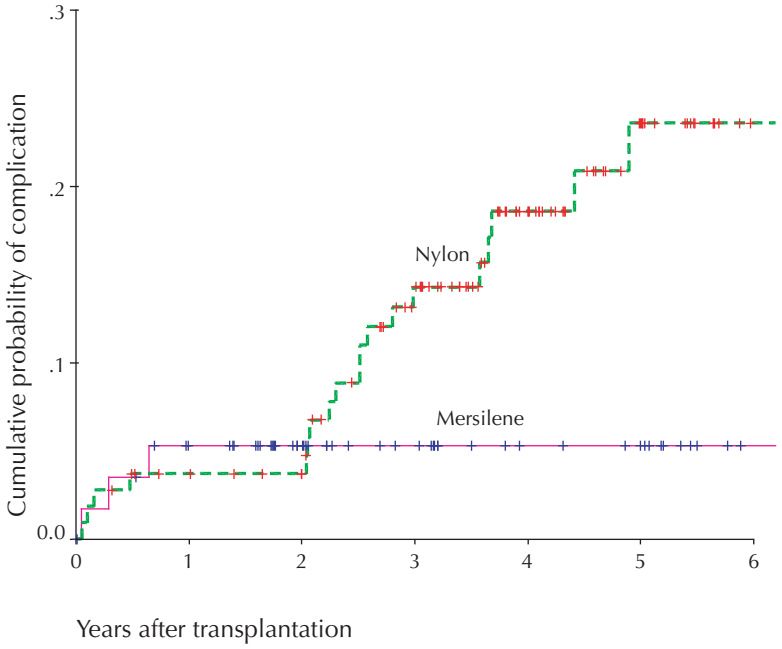

Figure 3. Cumulative probability of developing complications associated with broken or loose sutures (HR=0.50 with 95% CI 0.14-1.74).

The risk of developing a complication, regardless of type, was three times higher for the Mersilene group (HR = 3.24, with 95% CI 2.10-4.99). The risk of developing neovascularization, loose or broken sutures, epithelial defects, filaments or wound dehiscence, was not significantly different for the two groups (according to individual evaluation of each complication by Cox regression analysis).

Among the group of more serious complications (endophthalmitis, neovascularization, infiltration and wound dehiscence) there was no significant difference between suture groups (HR for Mersilene sutures was 1.82 with 95% CI 0.86-3.84). Endophthalmitis was seen in three eyes with Nylon sutures, from which two were related to a broken suture. The other case was caused by a bacterial keratitis. None of the eyes in the Mersilene group developed endophthalmitis. There was a tendency towards a lower risk of complications associated with loose or broken sutures in the Mersilene group (HR = 0.50 with 95% CI 0.14-1.74). This was especially pronounced after two years (Figure 3). No complications due to broken or loose sutures appeared in the Mersilene group after one year.

Some eyes experienced loose or broken sutures and infiltrates more than once. The yearly complication rate for loose or broken sutures, however, did not differ between the Mersilene group relatively to the Nylon group (Rate ratio (RR)

= 1.12 with 95% CI 0.70-1.79). The yearly rate for infiltrates was significantly higher for the Mersilene group (RR = 4.64 with 95% CI 1.29-16.680).

DISCUSSION

A significantly lower astigmatism was observed during the first two years after transplantation in transplants sutured with Nylon compared to transplants sutured with Mersilene. The risk of developing complications such as infiltrate, metaplasia and cheesewiring was higher in the Mersilene group. Our clinical impression, that transplants sutured with Nylon are prone to develop serious complications, such as endophthalmitis, was confirmed. Using Mersilene sutures, however, did not reduce the risk of developing serious complications during mid-term follow-up. There are, however, some indications that this might not be the same in late-term control since after two years there were fewer complications associated with loose or broken sutures in the Mersilene group.

This study provides a longer follow-up and a higher number of patients compared to other studies evaluating the effect of Mersilene sutures in corneal transplantation.[19-26] Previous studies evaluating Mersilene sutures in corneal transplants were conducted on eyes with a variety of pathologies. We felt that, to properly be able to compare the effect of Mersilene versus Nylon sutures, a more homogeneous group of patients was required. For this reason, in this study only primary transplants for Fuchs' endothelial dystrophy were included. This is the only study comparing transplants sutured with either Mersilene or Nylon filaments, in which no combination technique of interrupted Nylon sutures with a running Mersilene or Nylon suture is used. To our opinion this is the most appropriate method to evaluate whether complications are associated with Mersilene or Nylon.

A drawback of this study was that eyes were not randomized to either the Nylon or Mersilene suture group. The decision for suture type was merely based on the current preference of the surgeon; however, all surgeons were equally represented in both suture material groups. After encountering a complication with the use of Nylon sutures, a surgeon could be expected to change his preference to Mersilene sutures and vice versa. However, no preoperative patient factors were observed to influence this decision. Further, average length of follow-up was different in both groups. To correct for this, we used survival statistics, which adjust for follow-up time, to evaluate the risk of developing complications. Transplants are excluded from further analysis with survival statistics after an event has occurred. However, certain events can occur more

than once without interfering with transplant survival. To obviate this problem the yearly complication rate of complications that occurred more than once in one transplant was calculated. Results of this analysis, however, resembled those of the Cox regression analysis. A possible bias to the study results was the use of conventional keratometry to quantify astigmatism. This measures the astigmatism at a diameter of 3 mm from the center of the cornea. In case of irregular astigmatism, these measurements can be difficult and less useful.[27] Also, these measurements are not objective. Another weakness of this study was an unequal distribution in suturing techniques between the Nylon and Mersilene group, with relatively more interrupted sutures in the Mersilene group and more combined interrupted and running sutures in the Nylon group. Although there is no general agreement regarding which suture technique is the best to reduce astigmatism, it is obvious that suturing technique might play a role in postkeratoplastic astigmatism.[4,28,29] All statistical analyses were therefore adjusted for this variable.

Controversy consists about the use of Mersilene sutures in penetrating keratoplasty. Several studies conclude that Mersilene can be used effectively in corneal transplantation,[21-26] although these studies are non-comparative, evaluating the use of Mersilene sutures alone or in combination with Nylon sutures. A study by Ramselaar et al.,[26] comparing interrupted Nylon sutures combined with either a running Mersilene suture or a running Nylon suture, concluded that Mersilene appeared to be suitable for penetrating keratoplasty. In contrast to the aforementioned studies, Bertram et al.[20] concluded that Mersilene was inappropriate for use in penetrating keratoplasty because of its high incidence of complications. Our results are partly in concordance with those of the study of Bertram et al., with a higher risk of complications in the Mersilene group, as we noted a higher risk of metaplasia among these patients. This was also described by Frueh et al..[23] Furthermore, we confirmed the higher risk of cheesewiring among eyes in the Mersilene group.[20] As shown by others, suture removal after penetrating keratoplasty is not always an uneventful procedure. Removal of Nylon sutures even more than one year postoperatively can cause an unpredictable change in astigmatism, or even wound dehiscence, followed by choroidal hemorrhage.[11-13,30] This was confirmed in the 61 eyes (56.5%) of our Nylon suture group, where either the running Nylon suture or all Nylon sutures (in 21 eyes) were removed at the end of follow-up. Wound dehiscence or an increase in astigmatism of more than 3 diopters occurred in 13 (21.3%) of the 61 eyes, whereby another 2 eyes (3.3%) even developed an expulsive choroidal haemorrhage after suture removal.

The slightly lower astigmatism in the Mersilene group after 3 years follow-up may be explained by the increase in astigmatism after suture removal in the Nylon group in this period. In the early postoperative period, however, more surgical corrections for astigmatism and wound dehiscence were necessary in the Mersilene group. This may have been due to the inelasticity of Mersilene and the difficulties to handle Mersilene during surgery, resulting in too tight or too loose sutures. Transplants sutured with single running Mersilene sutures needed surgical intervention in all four cases. Handling sutures is more critical in a running suture technique than in an interrupted suture technique. Too tight sutures may cause postoperative cutting of the recipient and donor cornea, with subsequent complications due to loose sutures. Nylon sutures are easier to control during surgery and cause fewer problems in the early postoperative period. After 2 years, however, in contrast to Mersilene, Nylon sutures start to degrade allowing for spontaneous breakage. This was illustrated in our finding that no complications due to broken or loose sutures appeared in the Mersilene group after more than one year, in sharp contrast to the Nylon group. It would be interesting to compare complications and astigmatism between both groups after all Nylon sutures are removed. Eventually, a significantly beneficial effect for Mersilene sutures could then possibly emerge.

Our study indicates that Mersilene sutures will certainly not solve all problems of postkeratoplastic astigmatism and suture-related complications. Considering that all transplants sutured with a single running Mersilene suture needed surgical correction shortly after transplantation, the use of only a Mersilene running suture should be discouraged. Also concerning the risk of developing complications, Mersilene sutures are shown to be less suitable in the first two postoperative years. Nylon sutures appear to be preferable to Mersilene sutures with regard to the control of astigmatism and complications during the first two years after transplantation. However, a tendency for a beneficial effect of Mersilene sutures regarding complications due to loose or broken sutures is observed after two years. Longer follow-up after which all Nylon sutures are removed or hydrolyzed is required to assess a possible beneficial effect of Mersilene sutures in penetrating keratoplasty. In the meantime, other techniques such as “mushroom shaped” keratoplasty[31] and posterior lamellar keratoplasty are being developed.[32] These techniques might help in solving the problem of wound dehiscence, (other) suture-related complications and postoperative astigmatism.

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CHAPTER 5

IMPLANTATION OF A TORIC PHAKIC INTRAOCULAR LENS TO CORRECT HIGH CORNEAL ASTIGMATISM IN A PATIENT WITH BILATERAL MARGINAL CORNEAL DEGENERATION

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ABSTRACT

We present a patient with marginal corneal degeneration and corneal astigmatism of more than 10.0 diopters (D). A toric phakic intraocular lens (IOL) of 7.0 D cylindrical power was implanted in both eyes to correct the high astigmatism. An uncorrected visual acuity of 20/40 was achieved in both eyes, and the best corrected visual acuity improved by 4 Snellen lines to 20/20 in both eyes. Refraction and visual acuity remained stable at 1.5 years postoperatively. Implantation of a toric phakic IOL can be an option to correct high corneal astigmatism even when the full corneal astigmatism can not be treated.

INTRODUCTION

Peripheral marginal degeneration of the cornea can lead to severe visual loss secondary to excessive astigmatism. Various techniques can be used to treat astigmatism. In the early stages, mild to moderate astigmatism can be corrected with spectacles and contact lenses. If marginal degeneration progresses to thinning of the peripheral cornea and results in severe astigmatism and contact lens intolerance, alternative methods are necessary.

Several surgical procedures have been used to treat astigmatism (eg, crescentic lamellar keratoplasty and excision of ectatic stroma), but the ideal treatment has not been found.[1,2] Laser in situ keratomileusis (LASIK) is acceptable for the correction of mild to moderate astigmatism[3] but is not appropriate in cases with high irregular astigmatism such as marginal degeneration, keratoconus and astigmatism that occurs after penetrating keratoplasty (PKP). These patients could benefit from phakic toric intraocular lenses (IOLs)[4] such as the Artisan phakic IOL, which is shown to correct high myopia with a stable and fairly predictable refractive outcome.[5,6] Artisan toric phakic IOLs are available with a cylindrical power up to 7.0 diopters (D) and are appropriate for treatment of high astigmatism.[7]

CASE REPORT

A 51-year-old man with peripheral marginal corneal degeneration was referred to us in 1996 with a best corrected visual acuity (BCVA) of 20/100. An examination in 1991 revealed a BCVA of 20/20 in both eyes with a refraction of –6.00 –5.00 X 87 in the right eye and –8.50 –5.00 X 115 in the left eye. Ocular history included a peripheral laser coagulation treatment in the left eye in 1988 for an asymptomatic peripheral retinal hole. The patient's high astigmatism resulted from bilateral marginal corneal degeneration present in the inferior cornea with some vascularization, consistent with the diagnosis of Terrien marginal degeneration. The medical history was unremarkable, and the patient did not have a collagen or vascular disease or an atopic constitution. Because of the patient's low visual acuity with spectacle correction at the time of presentation, the use of contact lenses to correct myopia and astigmatism was advised. With contact lenses, the visual acuity was 20/20 in the right eye and 20/30 in the left eye. Four years later, the patient experienced a further decrease in visual acuity despite contact lens correction to 20/50 in both eyes. He was unable to wear contact lenses for more then 2 hours a day.

Because of contact lens intolerance and inadequate visual acuity with spectacles, an alternative method to correct the high myopia and astigmatism was considered. Laser in situ keratomileusis was not a treatment option because of the high astigmatism and extreme thinning of the cornea from marginal degeneration. Implantation of the Artisan phakic IOL was discussed with the patient because of our long experience with this IOL and our 1-year experience with the Artisan toric phakic IOL.

The preoperative BCVA was 20/40 with –4.50 –10.75 X 81 in the right eye and 20/50 with –3.00 –13.00 X 115 in the left eye. Keratometry was 41.00/51.00D X 95 and 40.25/52.50 X 100, respectively. The endothelial cell count was 2244 cells/mm^2 in the right eye and 1756 cells/mm^2 in the left eye with a Topcon 2000 specular microscope. Both eyes had a 3.20 mm pupil in daylight that expanded to less than 5.50 mm in dark conditions. A-scan ultrasound showed axial lengths of 26.62 mm in the right eye and 26.40 mm in the left eye with anterior chamber depths of 4.02 mm and 3.91 mm, respectively. Based on the refractive data and limited by the 7.00 D maximum cylinder of the toric IOL, the appropriate toric IOL power was calculated with the Van der Heijde formula to be –5.50 –7.00 X 90 in the right eye with implantation in axis 171 and –4.00 –7.00 X 90 in the left eye, with implantation in axis 25. The optical zone of these lenses was 5.0 mm.

After the patient was counseled and informed consent was obtained, toric IOL implantation was performed uneventfully in the right eye and 3 weeks later in the left eye. Before surgery and retrobulbar anaesthesia, the desired axis location was marked on the sclera with a surgical marker guided by the reflected images of the Javal keratometer on the cornea. Myotic drops (pilocarpin 2%) were administered to prepare the iris for IOL fixation. A limbal beveled incision of 5.5 mm was made at 12 o'clock, and 2 more paracenteses were made at 10 o'clock and 2 o'clock. The anterior chamber was opened and sodium hyaluronate 1.0% (Healon®) was introduced to maintain depth and to protect the endothelium. After implantation, the IOL was fixated to the midperipheral iris stroma with an enclavation needle after it was positioned in the desired axis. At the end of the procedure, a slit iridotomy was performed at 12 o'clock to prevent angle-closure glaucoma and the Healon was manually irrigated. The incision was closed with a 10-0 nylon running suture.

Five days postoperatively, the uncorrected visual acuity (UCVA) in the right eye was 20/40 and the BCVA, 20/25 with +1.25 –3.25 X 102. Further ocular examination was unremarkable and the iris-claw IOL was well centered and stable, so surgery was performed in the left eye. Five days after surgery in the left eye, the UCVA was 20/40 and the BCVA was 20/25 with –3.25-1.25 X 73. At 75

Table 1. Preoperative and postoperative visual acuity, refraction, and keratometry in both eyes

	Right Eye			Left Eye		
	BCVA	Subjective refraction	Keratometry	BCVA	Subjective refraction	Keratometry
Preoperative	20/40	-4.50-10.75 X 81	41.00/51.00 X 95	20/50	-3.00-13.00 X 115	40.25/52.50 X 100
5 days postoperative	20/25	+1.25-3.25 X 102		20/25	-3.25-1.25 X 73	
18 months postoperative	20/20	-1.00-0.50 X 70	40.25/52.00 X 90	20/20	-3.00-0.75 X 125	39.75/52.5 X 95

BCVA, best corrected visual acuity

days in the right eye and 55 days in the left eye, the refraction remained stable with a UCVA of 20/40 and a BCVA of 20/25 in both eyes. After 6 months, the subjective refraction was –1.75 –0.75 X 15 in the right eye and –2.50 –0.75 X 139 in the left eye. At 1.5 years, the subjective refraction remained fairly stable at –1.00 – 0.50 X 70 in the right eye and –3.00 – 0 .75 X 125 in the left eye; the BCVA of 20/20 in both eyes (Table 1). The keratometry changed marginally from the preoperative readings (Table 1). The endothelial cell count was 2694 cells/mm^2 in the right eye and 1654 cells/mm^2 in the left eye.

DISCUSSION

Implantation of a toric IOL is an alternative treatment for the correction of high astigmatism. The result we achieved in this case was excellent. Based on the toric IOL's maximal correction of 7.00 D cylindrical power, the residual cylinder achieved in the subjective refraction was much lower than expected. The preoperative subjective refractive cylinder of –10.75 X 81 in the right eye and – 13.00 X 115 in the left eye changed after toric IOL implantation to –0.50 X 70 and –0.75 X 125, respectively, with almost no change in corneal astigmatism, according to keratometry readings. Correction of the cylinders along with correction of the residual myopia led to a BCVA of 20/20 in both eyes.

Annular lamellar keratoplasty (LKP) and corneal wedge excision have been performed in marginal corneal degeneration cases to control corneal astigmatism. Reports of annular LKP are restricted to a few cases; no large series have been reported.[2,8-10] Along with other authors, we found that this procedure is not an optimal treatment. The time required for visual rehabilitation with LKP is longer than with toric IOL implantation. Reports of corneal wedge excision show

a poor long-term reduction in astigmatism.[1,11,12] Laser in situ keratomileusis has proved to be an effective treatment in eyes with less than 2.0 D of astigmatism,[3] but it cannot adequately correct high astigmatism. In our patient with a thin cornea and high astigmatism, LASIK was not an option. Intraocular refractive surgery was probably the only suitable choice.

Lens extraction with IOL implantation is another option to correct high astigmatism and myopia. There are several case reports and studies of toric IOL implantation after lens extraction.[13-19] Toric IOL implantation after lensectomy results in the loss of accommodation, whereas with the Artisan toric IOL, accommodation is preserved. Rotational instability is a problem with toric IOLs in the capsular bag,[19,20] but rotation of the iris-claw IOL is less likely because of its firm fixation to the midperipheral iris stroma. The off-axis position of an iris-claw lens is caused by incorrect placement of the IOL in the axis during surgery. A greater incidence of postoperative retinal detachment is expected with IOL implantation after lensectomy.[21,22] We consider the phakic toric IOL a more favorable option to correct high astigmatism and myopia in a patient with a clear lens.

Another phakic IOL option is posterior chamber (PC) IOLs. The potential for long-term effects such as cataractogenesis and pigment dispersion with phakic PC IOLs is a serious concern,[23-25] as is endothelial cell loss with phakic iris-claw IOLs.[26] Gimbel and Ziémba[27] report on a case with moderate astigmatism of –2.25 in which a toric posterior phakic IOL was used. We chose the Artisan toric anterior chamber IOL because it was the only available toric phakic IOL at the time surgery was planned.

Limitations to the Artisan IOL are a cylindrical power up to only 7.00 D and an optical zone of 5.00 mm. In high myopia, a small optical zone may produce halo effects and glare in dim illumination conditions. Careful patient selection excluding those with a pupil diameter of more than 5.00 mm under scotopic conditions might prevent these side effects. The incidence of astigmatism greater than 7.00 D is low. As this case report illustrates, full correction of astigmatism is not necessary to achieve an excellent BCVA in a patient with marginal corneal degeneration. Possible explanations of this are that the correcting cylinder of the IOL is closer to the nodal point of the eye or that full correction of astigmatism is not necessary because of the extreme irregularity.

The toric Artisan IOL cannot be implanted through a small incision. This can result in induced astigmatism, adding a level of unpredictability to the final result. The induction of astigmatism was negligible compared with the high astigmatism already present in this patient, however, and a change of only 0.5 D in corneal astigmatism with an axis shift of 5 degrees was seen after the

procedure. With anterior chamber IOL implantation, there is a possible risk for damage to the endothelium but the endothelial cell loss is probably the result of the surgical procedure.[26,28,29] Extensive follow-up and accurate methods to evaluate mean endothelial cell count are necessary to determine the long-term effect of iris-claw IOLs on endothelial cell loss. In this patient, endothelial cell counts with the Topcon 2000 specular microscope revealed a small decrease in the left eye and a small increase in the right eye. This may reflect the inaccuracy of counting methods.

To our knowledge, there is only one report of the implantation of an Artisan toric phakic IOL to correct high astigmatism.[4] This high astigmatism occurred after PKP. We believe our patient is the first in whom high astigmatism from marginal corneal degeneration was corrected with the Artisan toric phakic IOL. Marginal corneal degeneration is usually a contraindication for corneal refractive surgery.[30,31] This patient's visual improvement might not have been achieved through more common methods of refractive surgery.

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CHAPTER 6

IMPLANTATION OF ARTISAN TORIC PHAKIC INTRAOCULAR LENSES FOR THE CORRECTION OF ASTIGMATISM AND SPHERICAL ERRORS IN PATIENTS WITH KERATOCONUS

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ABSTRACT

Purpose: To evaluate the correction of astigmatism and spherical ametropia in patients with keratoconus through implantation of an Artisan toric phakic intraocular lens (PIOL) (Ophtec, Groningen, The Netherlands).

Methods: Artisan toric PIOLs were implanted uneventfully in both eyes of three patients with keratoconus with clear central corneas and contact lens intolerance.

Results: Best spectacle-corrected subjective visual acuity after lens implantation was unchanged in one eye and improved in five eyes. Spherical equivalent refraction was significantly reduced in all eyes ($P = 0.03$). The safety index was 1.44.

Conclusions: The implantation of an Artisan toric PIOL may be an alternative for treating astigmatism and myopia in contact lens intolerant patients with keratoconus with clear central corneas. Especially in patients with associated myopia, this procedure is worth considering before planning a penetrating keratoplasty.

INTRODUCTION

Keratoconus is a non-inflammatory condition characterized by ectasia and thinning of the cornea, inducing myopia and astigmatism. The disease usually starts around puberty and progresses slowly and may stabilize at a later age. In the early stages, spectacles and contact lenses are the usual treatment of choice. If a patient becomes contact lens intolerant, treatment consists of penetrating keratoplasty (PK) or lamellar keratoplasty (LK). Although good visual results usually are achieved with PK in patients with keratoconus,[1] visual recovery after the operation is long.[2] Frequent postoperative follow-up and use of corticosteroids for a prolonged time are necessary, and high astigmatism is a major postoperative complication.

In view of this, other treatment modalities could be preferred in an attempt to delay or avoid PK in select patients with contact lens intolerance and clear corneas. The implantation of a toric phakic toric intraocular lens might be a surgical alternative, especially as high myopia and an anterior chamber depth >3.0 mm often are associated with keratoconus.[3] The Artisan toric phakic intraocular lens (PIOL) (Ophtec, Groningen, The Netherlands) has been shown to correct high ametropia and astigmatism with a stable and fairly predictable refractive outcome.[4] Artisan toric PIOLs are available with a cylindrical power of up to 7.0 diopters (D) and a spherical power ranging between –3.0 and -23.5 D for myopia and +1 and +12 D for hyperopia. Therefore, these lenses can be used to correct high astigmatism and ametropia present in keratoconus. This article presents three contact lens intolerant patients with keratoconus with clear central corneas who were treated with the Artisan toric PIOL in both eyes.

METHODS

Artisan toric PIOLs were implanted between May 2002 and April 2003 in six eyes of three patients with keratoconus. All patients had a clear central cornea, were contact lens intolerant in at least one eye, and requested refractive surgery. After informed consent was given, patients underwent implantation of an Artisan toric PIOL. The Artisan toric PIOL is an iris-fixated anterior chamber implant of Perspex CQ-UV polymethylmethacrylate with ultraviolet filtration. Its overall diameter is 8.5 mm and the optical zone diameter is 5.0 mm. As some surgeons prefer to insert the lens through a temporal incision and to allow optimal implantation to the correct axis, two models are available. In Model A the axis runs

through the claws 0º and in Model B the axis is perpendicular to the line that runs through the claws (90º).

Pre- and postoperative examination of all patients included slitlamp biomicroscopy, determination of best spectacle corrected visual acuity (BSCVA), manifest refraction, tonometry, keratometry (autokeratometer), measurement of mesopic pupil diameter (Colvard pupillometer), endothelial cell count (non-contact specular microscopy, Topcon SP-2000 P, Tokyo, Japan), A-scan biometry (measurement of the anterior chamber depth) and indirect ophthalmoscopy. Exclusion criteria were uveitis, previous corneal or intraocular surgery, and systemic disease. The normally used exclusion criterion in refractive surgery of endothelial cell count < 2000 cells/mm^2 was not an absolute exclusion criterion in our study with pathologic corneas. Four days before surgery, patients were asked to apply indometacine 0.1% four times daily in both eyes. Surgery was performed under general anaesthesia by one surgeon (C.B.). Lenses were implanted in both eyes of one patient simultaneously, with a change of gloves and use of separate sets of surgical instruments for the second eyes. The surgical technique followed standard protocol as described in the toric PIOL European Multicenter Study.[4] A 5.5 mm corneoscleral incision was made superiorly and two paracenteses were made at 10 and 2 o'clock. After instillation of a cohesive viscoelastic fluid (Healon GV; Pharmacia & Upjohn, Kalamazoo, Mich), the Artisan toric PIOL was implanted and enclavated onto the iris. The enclavation sites on the iris were marked before surgery with an argon laser. An iridotomy was performed at 12 o'clock to prevent angle-closure glaucoma. The incision was closed with a 10-0 nylon running suture. On discharge patients were prescribed predmycine (Allergan, Antwerpen, Belgium) eyedrops four times daily and a combination of dexamethasone/neomycine/polymyxine ointment to be applied at night for 2 weeks. The appropriate power of the toric PIOL was calculated using the Van der Heijde formula.[5]

Follow-up took place 2 days, 2 weeks, 6 weeks and 6 months after surgery. At follow-up, patients were asked to report subjective complaints, such as monocular diplopia, halos or glare. Patients were asked to rate their overall satisfaction with their vision after implantation on a scale from 1 to 5 (with 1 being very poor and 5 being excellent). To analyze safety index (mean postoperative BSCVA / mean preoperative BSCVA) and efficacy index (mean postoperative uncorrected visual acuity / mean preoperative BSCVA), Snellen visual acuity was converted into logarithm of the minimum angle of resolution notation to calculate the mean and then transformed back into Snellen visual acuity. Vector analysis was used to analyze surgical-induced refractive correction.[6,7] For this purpose, preoperative and 6-months BSCVA refraction results were used. To analyze surigical-induced

corneal astigmatism (ie, incisional-induced astigmatism), vector analysis of pre- and postoperative keratometric values was used.[6,7] Student paired *t* test ($P < 0.05$) was used to analyze the change in spherical equivalent refraction after implantation.

RESULTS

Implantation of the Artisan toric PIOL was performed uneventfully in all six eyes. Preoperative patient characteristics are shown in Table 1. Preoperatively, intraocular pressure was normal in all eyes (range: 9 to 16 mmHg). No patient had evidence of cataract or had undergone prior ocular surgery. Funduscopy revealed myopic atrophy in the third patient. Contact lens intolerance was present in all patients. Contact lens wear had to be discontinued in the third patient due to the development of corneal neovascularization. All patients had keratoconus and a transparant central cornea. Probably due to the high refractive error and corneal irregularities, there was a low repeatibility between different preoperative keratometric and objective refraction measurements in the left eye of the last patient, making appropriate power calculations of the toric PIOL difficult. Moreover, the lens power required by the third patient was not available. She was therefore given the strongest available lens. Follow-up ranged from 6 months to 1 year. Postoperative BSCVA was stable from 6 weeks onward and improved in five eyes and remained unchanged in one eye. Preoperative and 6-months follow-up refractive data are presented in Table 2. The safety index was 1.44 and the efficacy index was 1.24. Preoperative spherical equivalent refraction was –13.88 D (range: –4.00 to –29.00 D). Mean spherical equivalent refraction

Table 1. Characteristics of study patients with keratoconus who underwent implantation of an Artisan toric phakic intraocular lens

Patient/ Sex/ Age	Eye	ACD (mm)	Endothelial cell count (cells/mm^2)	Axial length (mm)	Mesopic pupil (mm)
1/M/27	R	3.56	1625	23.64	4
	L	3.79	2384	24.06	4
2/M/26	R	3.91	3100	25.36	5
	L	3.45	2900	24.04	5
3/F/44	R	3.45	2300	30.11	4.75
	L	3.56	1800	29.94	4.75

ACD, Anterior Chamber Depth

Table 2. Preoperative and 6- month postoperative refractive data of patients with keratoconus who underwent implantation of an Artisan toric phakic intraocular lens

			Preoperative			Postoperative (6 months)			
Patient/ Eye	PTIOL power	Axis	BSCVA	SR	keratometry	BSCVA	SR	keratometry	ECC
1/R	-12 – 5.5 x 0	15	20/50	-11 – 6 x 15	52.87/58.37 x 111	20/30	0 – 2.5 x 45	52.87/57.37 x 105	3500
1/L	-3.5 – 5 x 0	135	20/30	-3 – 4.5 x 135	46.25/50.75 x 47	20/30	-1 – 2 x 105	46.00/50.25 x 46	2558
2/R	-4 – 2 x 0	45	20/25	-3 – 2 x 63	41.25/42.87 x 120	20/20	plan	41.37/43.00 x 115	3200
2/L	-4 – 3 x 90	28	20/50	-3.5 – 3 x 118	41.50/44.37 x 49	20/30	1 – 1.50 x 164	41.25/44.50 x 44	2800
3/R	-21 – 2 x 90	155	20/40	-24.5 – 3 x 65	48.75/51.00 x 121	20/25	1	45.75/47.25 x 129	2500
3/L	-21 – 2 x 90	175	20/60	-27 – 4 x 85	47.00/51.25 x 30	20/40	1.25 – 2 x 153	45.75/47.00 x 31	2100

PTIOL, phakic toric intraocular lens; BSCVA, best spectacle corrected visual acuity; SR, subjective refraction; ECC, endothelial cell count

Table 3. Surgical-induced refractive correction and incisional-induced corneal astigmatism

Patient/Eye	Surgical-induced refractive correction	Incisional-induced corneal astigmatism
1/R	-10.14 – 5.22 x 3	1.44 x 41
1/L	-1.30 – 3.90 x 148	0.52 x 145
2/R	-3.00 – 2.00 x 63	0.28 x 74
2/L	-3.55 – 3.40 x 104	0.65 x 19
3/R	-25.50 – 3.00 x 65	0.91 x 17
3/L	-26.44 – 5.61 x 78	3.00 x 120

postoperatively was -0.29 D (range: +1.00 to –2.00 D). Reduction in spherical equivalent refraction was significant (P = 0.03). Postoperatively, four of the six eyes were within ± 1.00 D of emmetropia. The average magnitude of refractive astigmatism was -3.75 D (range: –2.00 to –6.00 D) preoperatively and –1.33 D (range: 0 to –2.50 D) postoperatively. Incisional-induced corneal astigmatism and surgical-induced refractive correction are presented in Table 3. Based on the change in keratometry pre- and postoperatively the average incisional-induced cylinder was 1.14 D (range: 0.28 to 3.00 D).

None of the patients experienced pigment cell deposits on the crystalline lens or posterior synaechiae. Two patients reported mild glare (starburst or acuity

distortion noted at night but not interfering with function). No patient reported monocular diplopia. All patients were satisfied with the result. Mean subjective response for satisfaction was 4.17 using the previously described scale. All patients tolerate spectacle correction of the remaining refractive error.

DISCUSSION

Many patients with keratoconus can be succesfully fitted with modern contact lenses, which can reduce the number of patients requiring surgery. However, some patients cannot be corrected with contact lenses succesfully. Patients with globus cones, which may involve a large part of the cornea and may have a inferotemporally thinning in the periphery of the cornea, have trouble with contact lens fitting, and in these patients, a corneal graft may be more difficult to perform and frequently results in a high postoperative astigmatism. For these patients, the implantation of a toric PIOL can be an alternative to reduce spherical equivalent error and astigmatism. In our small study, visual acuity improved in almost all eyes compared to preoperative measures, and thereby at least postponed the need for PK. Because keratoconus is a progressive disorder, refraction is not expected to remain stable after the implantation of a toric PIOL. However, a PK in the future is unlikely to be negatively affected by the prior implantation of a PIOL. Furthermore, toric IOLs could be exchanged if necessary. Currently, patients with keratoconus and contact lens intolerance are primarily treated with PK or LK.[8-10] However, slow visual rehabilitation after keratoplasty is a disadvantage. Further surgical options such as laser in situ keratomileusis remain limited as keratoconus is considered a contraindication because of poor refractive stability and the risk of progressive keratectasis.[11,12]

In an effort to postpone or prevent PK and to shorten visual rehabilitation, various other surgical options have been investigated. Colin et al.[13] reported the results of INTACS inserts for keratoconus in 10 patients, and the Ferrara intrastromal corneal rings were used in a study on 26 patients by Siganos et al..[14] In both studies the spherical equivalent error and astigmatism were significantly reduced. However, the amount of possible reduction of myopia and astigmatism is probably less with INTACS or Ferrara intrastromal rings than with toric PIOLs. Especially in higher ametropia and astigmatism such as > –10 D myopia or > 2 D astigmatism, toric PIOLs might be a more suitable option. The large reduction of myopic error in our last patient would not have been possible with INTACS or Ferrara intrastromal corneal ring segments. Progression of the disease is not suspected to slow down after toric PIOL implantation. Although corneal

ring segments may reshape or reinforce the abnormal cornea, there is also no evidence that they can stop disease progression. Besides, the predictability of corneal implants in keratoconus is not yet high and a relative high residual refractive error might remain. Epikeratoplasty and LK have also been investigated as alternatives to PK for patients with keratoconus; owever, PK was found to be statistically superior with respect to visual outcome.[15,16]

Limitations of the Artisan toric PIOL are a cylindrical power of 7 D, a myopic power of 23.5 D and an optical zone of 5.0 mm. In high myopia, the small 5.0 mm optical zone may produce halo effects and glare in dim illumination conditions. Two of our patients reported glare after the operation; however, this complaint did not interfere with function. The reduction in spherical error in all six eyes was higher (87.4%) than the reduction in astigmatic error (64.5%), suggesting a high predictability for spherical errors, but a moderate predictability for astigmatic errors. This was partly caused by the limitation of maximum available spherocylindrical correction and may have also been caused by difficulty in measuring the astigmatism.

The Artisan toric PIOL cannot yet be implanted through an incision smaller than 5.5 mm. This can also result in induced astigmatism, adding a level of unpredictability to the final result. Dick et al.[4] reported a incisional-induced astigmatism of 0.53 D after implantation of toric PIOLs for correcting ametropia with astigmatism in nondiseased eyes. The contribution of the incisional-induced astigmatism to the level of unpredictability in our small study seems to be relatively low in five eyes (average 0.76 D). Only the left eye of the third patient had a large cylinder. This may be due to a low repeatibility of preoperative keratometry and refractive measures. Furthermore, the biomechanics of keratoconic corneas are not the same as those of normal corneas. Although keratometry results can also change due to progression of the keratoconus, it is difficult to analyze only the incisional-induced astigmatism. Progression of keratoconus leading to refraction change is a concern after implantation. Ideally, toric PIOL implantation should not be performed until keratometry and subjective refraction are stabilized. This implies that toric PIOL implantation should not be performed in recently diagnosed keratoconus or in younger patients with a progressive keratoconus. However, it is possible that there is no stabilization at any time.[17] A longer period of poor vision can have significant implication for young adults. After discussing the risk of an inadequate correction due to possible progression with the patient we believe that toric PIOL implantation is permitted if keratometry is not changed significantly over the past 6 months. Preoperative BCSVA should be at least 20/60, otherwise a PK is expected to have a superior visual outcome. Furthermore, patients are only good candidates for toric PIOL

implantation if subjective refraction is possible. This is typically complicated by the reduced repeatability of subjective refraction in patients with keratoconus compared to nondiseased eyes, as was certainly a problem in the left eye of the third patient.[18] An aveage subjective refraction, which was well tolerated by this patient was used for lens calculation. Moreover, there is a possible risk of damage to the endothelium, with anterior chamber IOL implantation. In our patients, however, we did not observe endothelial cell loss at 6 weeks postoperatively. Endothelial cell count in the right eye of the first patient was incredibly high after implantation compared to preoperative measurement. Inaccuracy of the present counting methods for pathologic corneas might also underlie the inconsistency in endothelial cell count among pre- and postoperative periods. Endothelial cell count might be misleading in patients with keratoconus because of an uneven distribution of endothelial cells. Contact lens wear for a prolonged time is related with higher pleomorphism and polymegatism of endothelial cells in patients with keratoconus.[19] With anterior chamber IOL implantation, there is a risk of damage to the endothelium. This remains a cause for concern. Studies on toric PIOL implantation in nondiseased eyes use endothelial cell count of $<2000/mm^2$ as an exclusion criteria.[4] We believe that in keratoconus eyes a lower cell density is also permitted if a PK is considered as the alternative to restore visual acuity. If PK becomes necessary after toric PIOL implantation, it is always possible to remove the lens at surgery. Implantation of a new Artisan toric lens after transplantation adjusted to postoperative refractive data is also an option.[20] A disadvantage of a possible earlier corneal decompensation after toric PIOL implantation would be a less favorable indication for transplantation (ie, bullous keratopathy instead of keratoconus).[1]

Our short-term results in this small series of patients are encouraging. Visual rehabilitation was rapid in all patients. No serious complications occurred. The implantation of a toric PIOL can be an alternative for correcting astigmatism and myopia in contact lens intolerant patients with keratoconus and clear central corneas. Long-term results and additional patients are needed to draw strong conclusions regarding the predictability for astigmatic correction and the influence of this procedure on the outcome of possible PK. In the meantime, especially in patients with associated myopia, this procedure can be worth considering before planning PK.

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CHAPTER 7

THE INFLUENCE OF INCISIONALLY INDUCED ASTIGMATISM AND AXIAL POSITIONAL ACCURACY ON THE CORRECTION OF MYOPIC ASTIGMATISM WITH THE ARTISAN TORIC PHAKIC INTRAOCULAR LENS

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Submitted

ABSTRACT

Purpose: To evaluate postoperative astigmatism with regard to incisionally induced astigmatism and deviation in axial alignment with the use of preoperative limbal marking with the Javal keratometer in eyes implanted with the Artisan toric phakic intraocular lens (IOL).

Design: Prospective nonrandomized trial.

Participants: Fifty-four eyes of 33 patients with myopia (mean –9.67 D) and astigmatism (mean –3.44 D).

Intervention: The enclavation site was marked on the limbus using the Javal Keratometer. The Artisan toric phakic IOL was then implanted according to the axis marked on the limbus. Follow-up was a minimum of 6 months.

Main outcome measures: Safety index, efficacy index, predictability and vector analysis of total refractive correction were determined. The effect of axis misalignment and incisionally induced astigmatism on the final results were evaluated.

Results: At 6 months postoperative the safety index was 1.29 ± 0.29 and the efficacy index was 1.04 ± 0.35. Mean spherical equivalent subjective refraction reduced from –11.39 ± 4.86 preoperatively to –0.38 ± 0.57 D at 6 months. Mean preoperative cylinder was 2.94 ± 1.47 D at an axis of 90.9°. At 6 months the mean cylinder was 0.28 ± 0.54 D at an axis of 174.3°. Vector analysis of total surgically induced astigmatism revealed a mean cylindric change of 3.21 ± 1.71 D. Average axis misalignment was 0.37 ± 5.34°. The mean incisionally induced astigmatism was 0.75 ± 0.61 D at 178.5 ± 26.2°.

Conclusions: Implantation of the myopic toric IOL leads to safe, efficacious and predictable results. The level of unpredictability caused by axis IOL misalignment has a minor effect on the residual refractive error. The procedure of axis alignment with the Javal keratometer appears to be an accurate method of marking the eye for toric IOL implantation. Incisionally induced astigmatism can result in an overcorrection of the cylinder. A systematic undercorrection of –0.50 D for attempted cylindric outcome could result in an achieved correction closer to emmetropia.

INTRODUCTION

Achieving emmetropia or other desired refractions is challenging when spherical ametropia is combined with astigmatism. Keratorefractive procedures with excimer laser have shown to be accurate for the treatment of mild to moderate myopia combined with astigmatism.[1] Among higher refractive errors, however, such procedures can lead to complications related to small optical treatment zones, preparation of the flap and to the irreversible weakening of the cornea.[2,3] Over the last few years, studies on diverse phakic intraocular lenses (IOLs) have demonstrated satisfactory results in the correction of high ametropia.[4-6]

The Artisan toric phakic (TP)IOL can be used for the combination of myopia and astigmatism. It is an iris-fixated anterior chamber implant of Perspex CQ-UV polymethylmethacrylate with ultraviolet filtration. Its overall diameter is 8.5 mm with an optical zone diameter of 5.0 mm. The myopic toric Artisan IOL is available in half diopter (D) increments with a cylindrical power up to 7.5 D and a spherical power from –3.0 to –23.5 D. Two models of TPIOLs are available to allow lens insertion through a temporal incision and to allow optimal implantation on the correct axis. In Model A, the axis runs through the claws at 0º and in Model B, at 90º.

Several studies published recently on the outcome of the TPIOL have demonstrated good results.[7-10] The Artisan lens has also shown to be rotationally stable.[8,11] A drawback of the lens, however, is that it requires an incision of 5.2 to 5.5 mm. This incision can induce corneal astigmatism.

Precise enclavation of the lens is paramount. Especially in higher degrees of astigmatism, minimal misalignment greatly reduces the corrective value of the lens, as approximately one third of the cylindric correction is lost if the IOL is rotated 10 degrees off axis.[12] Some surgeons mark the enclavation sites on the iris with the Argon or YAG laser.[7] Although this procedure appears to be accurate, laser burns can cause inflammatory reactions, iris bleeding or endothelial cell loss.[13,14] As laser burns have to be placed at least one week prior to lens implantation, they also create logistical efforts. Other surgeons use a digital image system, in which the axis is projected on the iris. This image can be used during surgery to find the correct lens position. At our center, the intended position of enclavation is marked on the corneal limbus using the Javal keratometer, directly prior to anaesthesia.

In this single center prospective study, we evaluate the safety, efficacy and predictability of the toric Artisan myopia phakic IOL. We further assess the influence of accurate axis lens placement using corneal markings with the Javal

keratometer and study the effect of astigmatism induced by the incision on the total surgically induced refractive correction of myopic astigmatism.

PATIENTS AND METHODS

Fifty-four consecutive eyes of 33 TPIOL patients were enrolled in this prospective study. Lens implantations were performed by one surgeon (GL) between 2000 and January 2004. Inclusion criteria consisted of the following: 1. General good health. 2. A minimum of 18 years of age. 3. Stable refraction for a minimum of one year 4. Astigmatism greater than 1.5 D combined with myopia 5. Absence of ocular pathology 6. Endothelial cell count greater than 2000 cells/mm^2 7. Anterior chamber depth greater than 3.0 mm (including corneal thickness) 8. Mesopic pupil size equal to or less than 5.0 mm. Informed consent in accordance with the Helsinki Declaration was obtained for each patient.

Prior to preoperative examination, patients were requested to discontinue contact lens wear for a minimum of 14 days to avoid the possibility of contact lens induced corneal warpage. The examination included best spectacle corrected visual acuity (BSCVA) in Snellen notation, slitlamp biomicroscopy, endothelial cell count (Topcon SP-2000-P), keratometry (autokeratometer, Topcon KR 7000P), A-scan immersion biometry, applanation tonometry, measurement of mesopic pupil diameter (Colvard pupillometer), and indirect ophthalmoscopy. Furthermore, objective refraction was measured with cyclopentolate hydrochlorate 1.0% eyedrops to exclude any accomodative error in subjective refraction. If large differences were found between the two refractive errors, subjective refraction was measured again. The power of the IOL, including the intended axis of enclavation, was calculated according to the Van der Heijde formula.[15]

Intended axes were marked preoperatively onto the corneal limbus with a surgical marker guided by the reflected images of the Javal keratometer. Myotic drops (pilocarpin 4%) were administered to prepare the iris for lens fixation. The intervention was performed under general or retrobulbar anaesthesia. A corneoscleral bevelled incision of 5.5 mm was made at the steep meridian and paracenteses were placed 8 mm apart at either side. The anterior chamber was opened and filled with viscoelastic fluid (Healon®) to maintain its depth and to protect the endothelium. After introduction of the lens into the anterior chamber with the holding forceps (Ophtec REF D02-70), it was positioned onto the desired axis and then fixed onto the midperipheral iris stroma with a disposable enclavation needle. A slit iridotomy was performed at 12 o'clock to prevent angle-closure glaucoma, whereafter the viscoelastic material was manually ir-

rigated. The incision was closed with a 10-0 nylon running suture. If both eyes were to be operated, interventions were separated by a minimum of two weeks. Postoperative treatment included ketorolac and dexamethasone 0.1% eyedrops four times a day for 4 weeks.

Follow-up examinations were scheduled at 1 day, 1 week, 1 month, 2 months, 6 months and 1 year after surgery and on a yearly basis thereafter. Postoperative examinations included slitlamp biomicroscopy, endothelial cell count (from 6 months postoperative onwards), keratometry, applanation tonometry, subjective and objective refraction, uncorrected visual acuity (UCVA) and BSCVA. Within the first 6 postoperative weeks, sutures were dissected or removed if they created undesirable corneal astigmatism. After 6 weeks, sutures were removed if they caused discomfort or had loosened. At 1 month follow-up, the Javal keratometer was used to determine the postoperative IOL axis alignment. Axis misalignment was defined as the difference between intended and achieved axis. The postoperative IOL position was measured without knowledge of the intended axis of implantation by one of the investigators (MB). Furthermore, patients were asked if they experienced halo or glare.

All data were collected prospectively from patient charts during follow-up examinations.

Statistics

To analyse BSCVA, UCVA, safety index (mean postoperative BSCVA / mean preoperative BSCVA) and efficacy index (mean postoperative UCVA / mean preoperative BSCVA), Snellen visual acuity was first converted into logarithm of the minimum angle of resolution (logMAR) notation to calculate the mean and then transformed back into Snellen visual acuity. Change in cylindrical refraction was calculated with vector analysis.[12]

Cylindrical refractions were transformed into double-angle vectors and rectangular coordinates, as described by Holladay.[12] The double-angle vector plots chart the cylinders horizontally (parallel, x-coordinates) and vertically (orthogonal, y-coordinates). After calculation, the horizontal and vertical components were transformed back to cylinders.

Total surgically induced refractive change in astigmatism was calculated with the use of vector analysis using cylindrical subjective refraction results.[12]

Incisionally induced astigmatism was defined as the vector of the change that occurred based on preoperative and postoperative keratometry values. In this analysis, eyes in which additional operations were performed after implantation were excluded to prevent possible bias (n = 3). Furthermore the one eye with

a Model B lens implantation was also excluded, as it was the only eye with an incision on the flat axis.

Comparison of data between preoperative and postoperative periods were performed with Student t-test for paired data using a level of significance of p = 0.05. A likelihood test was performed to evaluate the stability of refractive results during follow-up.

RESULTS

Patient population

All 54 eyes of the 33 patients were followed-up for a minimum of 6 months. At one year, follow-up data was available for 45 eyes of 27 patients and at two years, 20 eyes of 14 patients. Mean follow-up was 17.1 ± 11.4 months. Twenty-three of the 33 patients were female (69.7%). Mean age was 39.5 ± 2.0 years (range: 19 - 57 years). Average axial length was 27.34 ± 0.27 mm (range: 23.72 - 32.54 mm) and average anterior chamber depth was 3.66 ± 0.31 mm (range: 3.18 - 4.32 mm). Mesopic pupil diameter averaged 4.7 ± 0.9 mm (range: 3.0 –7.0 mm). Surgery was performed with the use of retrobulbar anaesthesia with the exception of 13 eyes of 7 patients where surgery was performed under general anaesthesia. Model A was implanted in 53 eyes and Model B in 1 eye.

Table 1. Preoperative and postoperative refractive results

	Preoperative	Postoperative		
	(54 eyes, 33 patients)	6 months (54 eyes, 33 patients)	12 months (45 eyes, 27 patients)	24 months (20 eyes, 14 patients)
SE (mean) ± SD (D), (range)	-11.39 ± 4.86, (–2.13 to -25.63)	-0.38 ± 0.57, (-2.25 to +0.75)	-0.44 ± 0.62, (-2.75 to +0.50)	-0.44 ± 0.51, (-2.13 to 0.00)
Mean vectorial astigmatism (D) x axis	2.94 ± 1.47 x 90.9°	0.28 ± 0.54 x 174.3°	0.23 ± 0.54 x 173.9°	0.26 ± 0,43 x 175.4°
Mean UCVA ± SD		0.72 ± 0.28	0.70 ± 0.28	0.75 ± 0.26
Mean BSCVA ± SD	0.71 ± 0.23	0.88 ± 0.23	0.85 ± 0.25	0.94 ± 0.25
± 1.00 D of emmetropia (%)	-	88.9	90.7	95.0
± 0.50 D of emmetropia (%)	-	66.7	65.1	70.0
Loss ≥ 2 lines BSCVA	-	0	1 (2.2%)	0
Gain ≥ 1 line BSCVA	-	40 (74.1%)	33 (73.3%)	14 (70.0%)

SE, spherical equivalent refraction; UCVA, uncorrected visual acuity; BSCVA, best spectacle corrected visual acuity

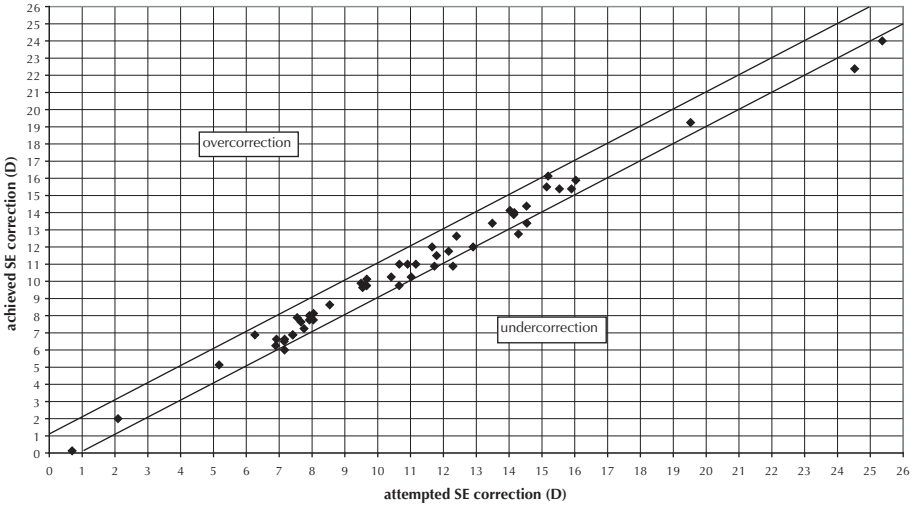

Figure 1. Attempted spherical equivalent versus achieved subjective spherical equivalent at 6 months postoperative.

Visual acuity and refraction

Preoperative refractive measurements are presented in Table 1, along with the postoperative spherical equivalent (SE) of subjective refraction, UCVA, BSCVA and percentages of eyes within ± 1.00 D or ± 0.50 D of emmetropia at 6 months, 1 year and 2 years. The deviation of the achieved SE correction from attempted SE correction at 6 months is presented in Figure 1. Average BSCVA improved significantly after implantation with 0.71 ± 0.23 preoperatively to 0.88 ± 0.23 at 6 months ($p < 0.001$). A gain of one or more BSCVA lines was seen in 74.1% of the eyes at 6 months. The safety index after 6 months and 1 year was 1.29 and 1.26, respectively. The efficacy index was 1.04 at 6 months and 1.02 at one year.

Surgically and incisionally induced astigmatism

The mean preoperative astigmatism using vector analysis was –2.94 ± 1.47 D for the horizontal component (x) and –0.09 ± 1.52 D for the vertical component (y), equivalent to a cylinder of 2.94 ± 1.50 D at an axis of 90.9°. A double-angle minus cylinder plot of preoperative subjective cylinder is presented in Figure 2. At 6 months, the total surgically induced refractive change was 3.21 ± 1.71 D at an axis of 0.3°. Based on the amount of cylindric correction of the implanted IOL, average attempted cylindric outcome was –0.14 D at 180º. Mean achieved postoperative astigmatism at 6 months was + 0.28 ± 0.57 D for x and -0.06 ± 0.51 D for y, translating to a cylinder of +0.28 ± 0.54 D at a mean axis of 174.3°

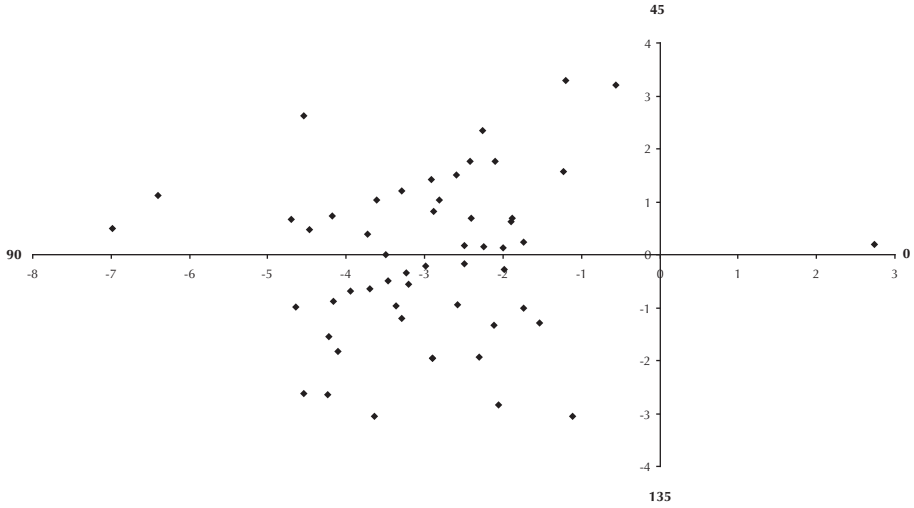

Figure 2. Double-angle plot of minus cylinder of subjective preoperative refraction.

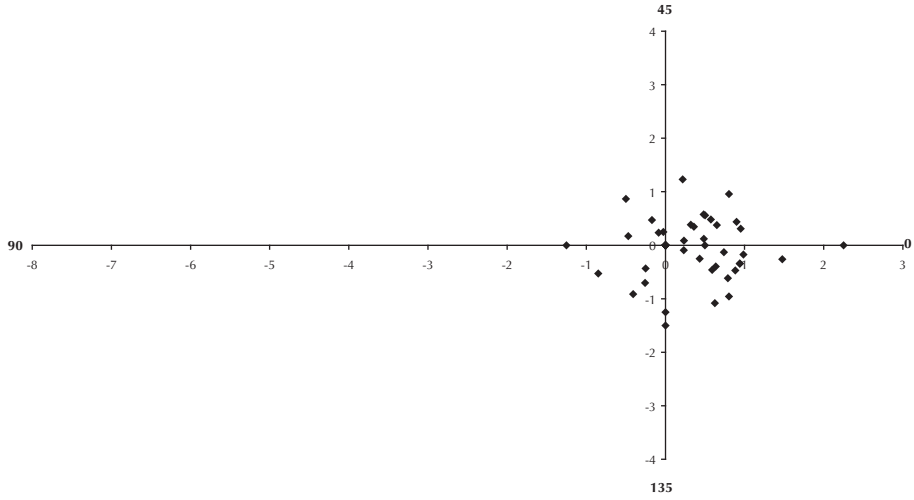

Figure 3. Double-angle plot of minus cylinder of subjective refraction 6 months postoperatively.

(Figure 3). There was no significant difference in postoperative astigmatism during all the follow-up periods (likelihood ratio test, $p = 0.47$).

From 2 months postoperative, keratometric data remained stable (Figure 4). Suture removal at any time after 2 months did not significantly influence keratometric data. Average incisionally induced astigmatism calculated after 2 months was + 0.75 ± 0.61 D at a mean axis of 178.5°. Considering this incisionally

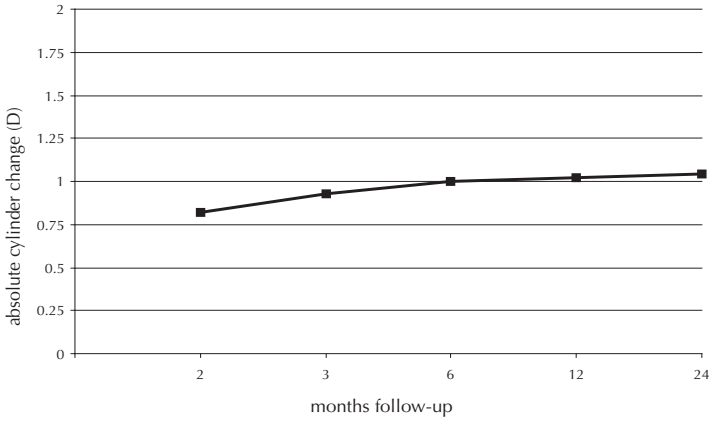

Figure 4. Mean absolute incisionally induced astigmatism in diopters at different follow-up periods.

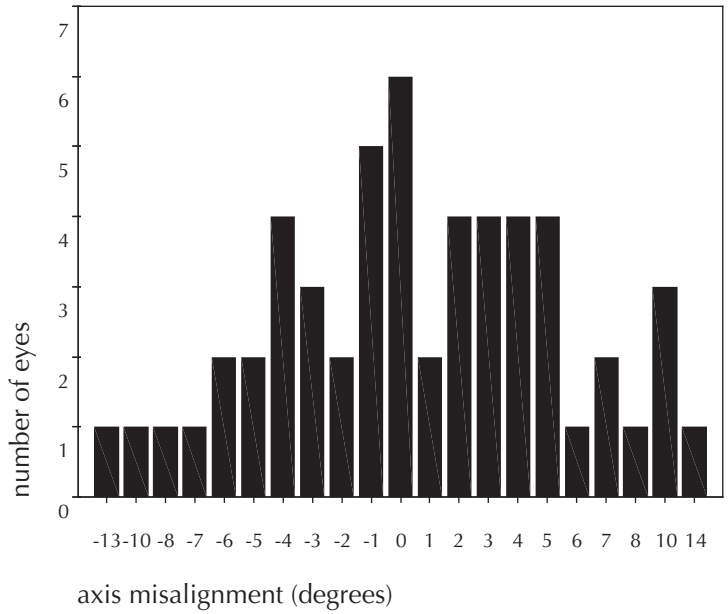

Figure 5. Postoperative deviation in attempted axis of enclavation per eye.

induced astigmatism, mean expected cylindric outcome changed from –0.14 D at 180° to + 0.61 D at an axis of 178.1°.

Axis misalignment

The mean difference between the achieved and the intended axis alignment of the lens was 0.37 ± 5.34° (range -13 to +14°). The mean absolute deviation was

4.15 ± 3.34°. Axis misalignment is presented in Figure 5. The position of an IOL with a cylindric correction of –7.0 D had to be changed in one eye due to a residual cylinder of –1.75 D at 130º in combination with an axis misalignment of 8°. After changing the IOL position, the residual cylinder decreased to -0.50 D at 65°. An axis misalignment of more than 10º was seen in two eyes only. The correcting cylinders of these toric IOLs were –2.00 and –3.00 D. In the first of these two eyes, no subjective residual astigmatism was seen, despite an axis deviation of 14º. In the second eye, a deviation of -13º from the target axis was found, resulting in a residual subjective cylinder of –1.00 D.

The average (absolute) spectacle cylindric error as a result of axis misalignment was calculated to be 0.16 ± 0.12 D. The attempted cylindric correction, -0.14 D at 180º, changed marginally to –0.15 D at 180º, when the known axis deviation for each lens was accounted for.

Endothelial cell loss

Mean preoperative endothelial cell count was 2724 ± 388 cells/mm^2 (range: 1577 - 3463). Mean postoperative endothelial cell count was not significantly different from mean preoperative endothelial cell count with 2779 ± 458 cells/mm^2 (range: 1658 - 3784) at 6 months, 2783 ± 475 cells/mm^2 (range: 1658 - 3591) at 1 year and 2717 ± 356 cells/mm^2 (range: 2249 - 3344) at 2 years (Paired t-test, $p > 0.45$).

Complications

Intervention was uneventful in all patients. One patient developed a wound leak after suture removal at one week, requiring resuturing of the incision. One patient, with a preoperative asymptomatic retinal break treated with Argon laser, developed a retinal detachment 10 days after surgery. At 1 year follow-up, BSCVA in this eye was 0.40, compared to 0.50 preoperatively.

The mean preoperative intraocular pressure (IOP) was 15.3 ± 3.4 mmHg. Seven eyes developed a temporary IOP rise above 21 mmHg within the first month of surgery (range: 22-30 mmHg), although it normalized in all eyes after discontinuing topical corticosteroids. The mean postoperative IOP over all follow-up periods (15.7 ± 3.4 mmHg) did not differ significantly from the preoperative values ($p > 0.25$).

One eye in the study experienced a significant loss of lines after developing cataract one year postoperatively. Visual acuity decreased from 0.4 preoperative to 0.2 postoperative. To our knowledge, surgery had been uneventful.

No pigment dispersion or pupillary block occurred in any eyes during the follow-up period. Seven of the 33 patients noted having more difficulty with

haloes or glare postoperatively. Only one of the patients with such a complaint had a mesopic pupil size greater than 5 mm. All patients were satisfied with the outcome of surgery. No patient considered removal of the lens.

DISCUSSION

The safety, efficacy and predictability of phakic toric Artisan lens implantation for the correction of myopia and astigmatism in this study were high. The toric Artisan lens was investigated before in a large European Study. The effect of axis misalignment and incisionally induced astigmatism on the final outcome were not analyzed in that study by Dick et al.. In our study we demonstrated that the intended astigmatism correction was a slight undercorrection of 0.14 D. The final result of the astigmatism correction was, however, an overcorrection of 0.28 D. We analyzed the effect of incisionally induced astigmatism and axis misalignment on the refractive outcome. We found that we introduced an against the rule astigmatism of 0.75 D by making the incision of 5.5 mm at the steep axis. This induced astigmatism is also known to result after cataract surgery.[16,17] Taking into account the incisionally induced astigmatism, the expected cylinder outcome was a 0.61 D overcorrection. Instead of this amount we observed a smaller overcorrection of 0.28 D. Besides incisionally induced astigmatism, axis misalignment can also create unpredictability to the final result. Proper surgical alignment of the IOL is a prerequisite for the success of TPIOL implantation. Due to the firm fixation of the Artisan lens to the midperipheral iris stroma, rotation of the lens has not been observed. Hence, axial misplacement of an iris-claw lens is caused by incorrect alignment of the lens during the surgical procedure. We found an absolute axis deviation of 4.15 ± 3.34º, which is comparable with the deviation found in the study by Tehrani et al..[8] Although most surgeons use preoperative laser iridotomies to mark the axis, our center uses limbal marking with the use of the Javal keratometer. This method does not incur the risk of intraocular inflammation and can also prove to be practical for the surgeon, as the marking can take place directly preoperative, avoiding an extra patient visit. One disadvantage of this method, however, is that the marking can fade or disappear during preoperative preparation of the eye. We encountered this problem in one eye, resulting in a deviation of -14º from the intended axis. Another lens required realignment after developing a subjective postoperative cylinder of –1.75 D. The effect of the misalignment on the final cylindric outcome is however small. The mean attempted cylindric outcome of –0.14 D at 180º, changed marginally to –0.15 D at 180º, when the known axis error for each lens was accounted for.

Both incisionally induced astigmatism and axis misalignment could not explain the discrepancy between expected and achieved cylindric corrections. Several other factors could have influenced the achieved correction. Firstly, fixed factors such as the lens only being available in increments of half diopters and a calibration error of ± 0.3 D of the lens itself can decrease precision. Secondly, our data are based on subjective refraction results. Our clinical impression is that patients tend to experience less astigmatism than objectively observed, subsequently the subjective cylindric correction is lower.

Refractive results in this study were, however, predictable and efficacious and resemble those achieved with LASIK in lower degrees of myopia and astigmatism.[1] Nearly ninety percent of the eyes in our study were within 1.00 D of emmetropia from 6 months onwards. These data compare favorably with LASIK results for moderate to high myopia and astigmatism, where studies report between 41% to 76% of eyes being within 1.00 D of emmetropia.[1,18-22] LASIK correction among higher refractive errors, however, tends to result in lower predictability.[23,24] Furthermore, the large amount of stromal tissue ablated during a LASIK procedure to correct these higher degrees of myopia and astigmatism predisposes eyes to corneal ectasia and associated visual problems.[25]

Another option for the correction of high myopia with astigmatism is clear lens extraction with toric IOL implantation. Studies have shown that implantation of a toric IOL after clear lens extraction carries a higher risk of retinal detachment and further results in the loss of accommodation in young patients.[26] Moreover, rotational stability may be a problem with toric IOLs in the capsular bag.[27] Compared to LASIK or clear lens extraction, the correction of moderate to high myopia combined with astigmatism appears to be safer and more predictable with phakic IOL implantation, where the degree of correction does less physically affect the eye. Among phakic IOL options are posterior chamber (PC) IOLs, which require a smaller incision (3.2 mm) for lens implantation compared with the 5.5 mm for the toric Artisan lens.[28-30] To our best knowledge, only one case report has been published on the result of a toric PCIOL for the correction of myopia combined with astigmatism.[31] The potential for cataractogenesis and pigment dispersion with these IOLs is a crucial long-term concern.[32,33] In our study, however, one patient also developed a cataract. Although myopia is a known risk factor for cataract development at an earlier age, it is unclear if intraocular surgery accelerated this process.

In our study, seventy percent or more of the cases exhibited a gain of one or more lines of BSCVA. Such improvements in visual acuity have also been reported in other studies[34,35] and have been attributed to the increase in the size of the retinal image compared to spectacle correction.[36]

Successful correction of myopia and astigmatism with a TPIOL depends on several variables. In this study, we not only report the accuracy of the refractive results, but also the refractive contribution of variables such as the deviation between intended and achieved axis of implantation and the contribution of incisionally induced astigmatism. We believe that understanding these extra parameters allows greater insight into increasing the predictability of TPIOL implantation.

In conclusion toric myopic Artisan lens implantation leads to highly predictable, effective and safe results. Marking the enclavation site for TPIOL implantation with the use of the Javal keratometer appears to be a safe and reliable method. Predictability could be further increased by accounting for incisionally induced astigmatism. A systematic undercorrection of –0.50 D for attempted cylindric outcome is advised when using a corneoscleral incision of 5.5 mm.

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CHAPTER 8

TORIC PHAKIC INTRAOCULAR LENS FOR THE CORRECTION OF HYPEROPIA AND ASTIGMATISM AND MIXED ASTIGMATISM

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ABSTRACT

Purpose: To evaluate the Artisan toric phakic intraocular lens for the correction of hyperopia and astigmatism and mixed astigmatism.

Setting: Department of Ophthalmology, Erasmus MC Rotterdam, The Netherlands and Department of Ophthalmology, Sint Truiden, Belgium.

Methods: Prospective study on 50 eyes of 30 patients with hyperopia and astigmatism (n = 47) or mixed astigmatism (n = 3). Artisan toric phakic intraocular lenses were implanted between April 1999 and June 2004. We analyzed uncorrected visual acuity, best-corrected visual acuity, refraction, astigmatism, safety and predictability. Change in astigmatism was analyzed with vector analysis.

Results: Mean preoperative Spherical Equivalent was +4.23 ± 2.26 D in the hyperopic group and –1.21 ± 0.50 D in the mixed astigmatism group. Mean follow-up was 11.6 months (range: 6.0 - 37.0). A gain of one or more lines BSCVA was seen in 36%. Safety index and efficacy index after 6 months were 1.06 and 0.82, respectively. The mean postoperative astigmatism at 6 months was 0.24 D at an axis of 150º. At 6 months about three-quarters (76%) of the eyes had an uncorrected visual acuity of 20/40 or better. Two eyes lost 2 or more lines BSCVA. In 2 eyes the lens position had to be changed because of a large axis misalignment. No serious complications developed in any of the treated eyes during follow-up.

Conclusions: Artisan toric phakic intraocular lenses can correct moderate to high hyperopia combined with astigmatism with good refractive results. In this study, there were no serious complications. However, the predictability of the refractive results appears to be lower as compared to the correction of myopia and astigmatism with toric Artisan lenses.

INTRODUCTION

Refractive surgery options to treat moderate to high hyperopia and hyperopic astigmatism are limited. Predictability and safety with either Laser in situ keratomileusis (LASIK) or Photorefractive keratectomy (PRK) is lower compared to the treatment of moderate myopia with or without astigmatism.[1,2] Reported complications are regression, corneal ectasia, epithelial ingrowth, irregular astigmatism and low predictability, especially in eyes with higher hyperopia or hyperopia combined with astigmatism.[3-6] Clear lens extraction with implantation of a toric intraocular lens has the disadvantage of accommodation loss in a younger age group. Phakic intraocular lenses can be an alternative for the correction of hyperopia and hyperopic astigmatism. Over the last few years, studies on diverse phakic IOLs have demonstrated satisfactory results to correct high ametropia.[7-10] Several studies have recently been published on the Artisan toric phakic intraocular lens (TPIOL) for the correction of ametropia with astigmatism.[11-13] The Artisan toric lens is an iris-fixated anterior chamber implant of Perspex CQ-UV polymethylmethacrylate with ultraviolet filtration. Its overall diameter is 8.5 mm and the optical zone diameter is 5.0 mm. Two models of the Artisan lens are available. In Model A the axis runs through the claws at 0º and in Model B the axis is perpendicular to the line that runs through the claws at 90º. In eyes with a preoperative cylinder axis between 0 and 45 degrees or between 135 and 180 degrees Model A is recommended. In eyes with a preoperative cylinder axis between 45 and 135 degrees Model B is recommended.

Studies on the toric Artisan lens mainly report the results of the correction of myopia with astigmatism. Differences between hyperopia and myopia that are important for refractive surgery are iris configuration, a shallower anterior chamber depth and limited improvement of best spherical corrected visual acuity postoperatively. The third is due to a smaller image size with corrected refraction closer to the eye's nodal point in hyperopic patients. In our opinion these differences justify a study evaluating solely the results of TPIOLs correcting hyperopia and astigmatism. The hyperopic toric Artisan lenses are available in half diopter increments with a cylindrical power up to 7.5 Diopters (D) and a spherical power from +2.0 to +12.0 D. In this paper we report the results of TPIOL implantation in 50 eyes of 30 patients with hyperopia and astigmatism or mixed astigmatism.

PATIENTS AND METHODS

We enrolled 50 consecutive eyes of 30 patients in this prospective study. Between April 1999 and June 2004 consecutive implantation of the TPIOL's was performed by two surgeons (GL and CB) in two separate clinics (Erasmus MC Rotterdam, The Netherlands and Sint Truiden, Belgium). Inclusion criteria consisted of general good health, 18 years of age or more, stable refraction for at least one year, astigmatism greater than or equal to 1.5 D combined with hyperopia, absence of ocular pathology, endothelial cell count more than 2000 cells/mm^2, anterior chamber depth more than 3.0 mm (including corneal thickness), no convex iris configuration and mesopic pupil size equal or less than 5.0 mm. Informed consent in accordance with the Helsinki Declaration was obtained for each patient.

Preoperative examination included slit lamp biomicroscopy, endothelial cell count (non contact specular microscopy, Topcon SP-2000-P), keratometry (Topcon KR-7000-P), A-scan biometry (Alcon), applanation tonometry, measurement of mesopic pupil diameter (Colvard pupillometer), indirect ophthalmoscopy and subjective and objective refraction. Objective refraction with cyclopentolate hydrochlorate 1.0% eye drops was measured to exclude any accommodative error in subjective refraction. If large differences were found, subjective refraction was performed again. Best spectacle corrected visual acuity (BSCVA) was also noted (Snellen). All patients were requested to discontinue contact lens wear at least 14 days before preoperative examination.

The power of the Artisan lens and the intended axis of enclavation was calculated based on keratometric readings, anterior chamber depth and subjective refraction error, according to the Van der Heijde formula.[14] Prior to surgery the desired axis location was either marked on the limbus with a surgical marker guided by the reflected images of the Javal keratometer on the cornea (GL) or the enclavation sites on the iris were marked with an argon laser at least one week before surgery (CB). Myotic drops (pilocarpin 4%) were administered to prepare the iris for lens fixation. Intervention was performed under general anaesthesia (all cases in Sint Truiden and some cases in Erasmus MC) or retrobulbar anaesthesia (Erasmus MC). A corneoscleral bevelled incision of 5.5 mm was made at the steepest axis for Model A and at the flattest axis for Model B and paracenteses were placed at either side, 8 mm apart from each other. The anterior chamber was opened and introduced with viscoelastic fluid (Healon®/Healon GV®) to maintain its depth and to protect the endothelial cell layer. After introduction of the lens into the anterior chamber with the holding forceps, it was positioned onto the desired axis and then fixed onto the midperipheral iris stroma with a

disposable enclavation needle. A slit iridotomy was performed at 12 o'clock to prevent angle-closure glaucoma, whereafter the viscoelastic material was manually irrigated. The incision was closed with a 10-0 nylon running suture. Postoperative treatment included dexamethasone 0.1% or predmycine® eye drops and ketorolac eye drops four times a day for 4 weeks.

Follow-up examinations were scheduled at 1 day, 1 week, 1 month, 2 months, 6 months and 1 year after surgery and on a yearly basis thereafter. Examinations included slit lamp biomicroscopy, endothelial cell count, keratometry, applanation tonometry, subjective and manifest refraction, UCVA and BSCVA. Within the first two postoperative months, sutures were removed depending on residual refractive astigmatism and change in topographic astigmatism. Furthermore, patients were asked about subjective complaints of halos and glare. All data were collected prospectively from patient charts during the follow-up examination.

Statistics

Refractive outcomes at 6 months and 1 year were analyzed. To analyse BSCVA, UCVA, safety index (mean postoperative BSCVA / mean preoperative BSCVA) and efficacy index (mean postoperative UCVA / mean preoperative BSCVA) Snellen visual acuity was first converted into logarithm of the minimum angle of resolution notation (logMAR) to calculate the mean and subsequently transformed back into Snellen visual acuity. Change in cylindrical refraction was calculated with vector analysis as described by Holladay et al.,[15] using subjective refraction results. To compare preoperative and postoperative astigmatism, the astigmatism vector computations were analyzed using Mixed Model ANOVA statistics (SAS software). The model was corrected for a possible inclusion of two eyes of one individual patient. The vector change in keratometric cylinder between preoperative and 6 months postoperative values was considered the astigmatism induced by the incision. For the analysis of incisionally induced astigmatism, eyes that underwent a second surgical intervention within 6 months after implantation were excluded (n = 2). Continuous variables were described with mean, standard deviation and range. Comparison of continuous data between preoperative and postoperative periods was performed with Student t-test for paired data. A level of significance of $p = 0.05$ was used.

RESULTS

Fifty eyes of 30 patients were included in this study. Preoperatively, all patients had clear lenses and no retinal pathology was noted. A certain degree of amblyopia

Table 1. Preoperative and postoperative endothelial cell count and refractive results

	Preoperative	6 Months follow-up (n = 50)	12 Months follow-up (n = 17)
ECC ± SD, (range)	3001 ± 362 (2100-3721)	2976 ± 350 (2059-3610)	3000 ± 177 (2700-3300)
SE (mean) ± SD, (range)	3.97 ± 2.54 (-1.75- + 8.88)	-0.125 ± 1.22 (-0.25 to 3.0)	0.21 ± 1.02 (-1.50 to 2.50)
Mean UCVA ± SD	-	0.55 ± 0.27	0.59 ± 0.31
Mean BSCVA ± SD	0.68 ± 0.16	0.72 ± 0.14	0.76 ± 0.11
± 1.00 D of emmetropia (%)	-	78.0%	82.4%
± 0.50 D of emmetropia (%)	-	48.0%	47.1%
UCVA ≥ 20/40		76.0%	82.4%
Loss ≥ 2 lines BSCVA (%)		4.0%	0%
Gain ≥ 1 line BSCVA (%)		36.0%	52.9%
Safety index		1.06	1.12
Efficacy index		0.82	0.87

ECC, endothelial cell count; n = number of eyes; SE, spherical equivalent; UCVA, uncorrected visual acuity; BSCVA, best spectacle corrected visual acuity

was observed in 21 eyes, but none of the eyes had a BSCVA of less than 20/60. Mean amplitude of the anterior chamber depth was 3.2 ± 0.2 mm (range: 3.0-3.8) and mean axial length was 21.6 ± 1.0 mm (range: 19.5-23.7). Mean intra ocular pressure (IOP) was 15.5 ± 3.4 mmHg. Mesopic pupil diameter averaged 4.4 ± 0.9 mm (range: 3-6). Ten patients were male and 20 patients were female. Mean age (primary eye in bilateral subjects) was 37.0 years (range: 19.0–65.8). Mean preoperative hyperopic refraction was +5.71 ± 2.39 D and mean absolute refractive astigmatism was –3.48 ± 1.77 D. Mean preoperative endothelial cell count was 3001 ± 362 (range: 2100-3721). Follow-up ranged from 6 months to 3 years with an average of 11.6 months. All patients attended follow-up at 6 months. At one year, complete follow-up data were available for 17 eyes.

Preoperative refractive data are presented in Table 1 along with endothelial cell count and postoperative visual acuity and refractive results. Postoperative data are given at 6 months, otherwise this will be mentioned in the text. A gain of one or more lines in BSCVA occurred in 18 eyes (36%). About three-quarters (76%) of the eyes had an uncorrected visual acuity of 20/40 or better. At one year 14 of the 17 eyes (82.4%) had a visual acuity of 20/40 or better. Two eyes lost 2 lines and 3 eyes lost 1 line. One of the patients with a loss of 2 lines in BSCVA had complains of halos and glare. We could not find an explanation for the loss of 2 lines in BSCVA in the second eye. According to vector analysis adjusted for two eyes per patient the mean preoperative astigmatism was 2.36 ± 2.26 D at

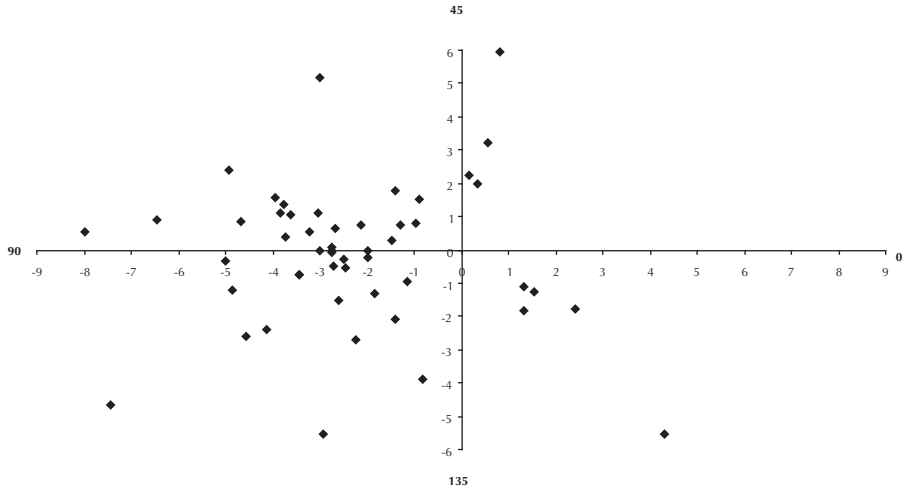

Figure 1. Double angle minus cylinder plot of preoperative refractive cylinders.

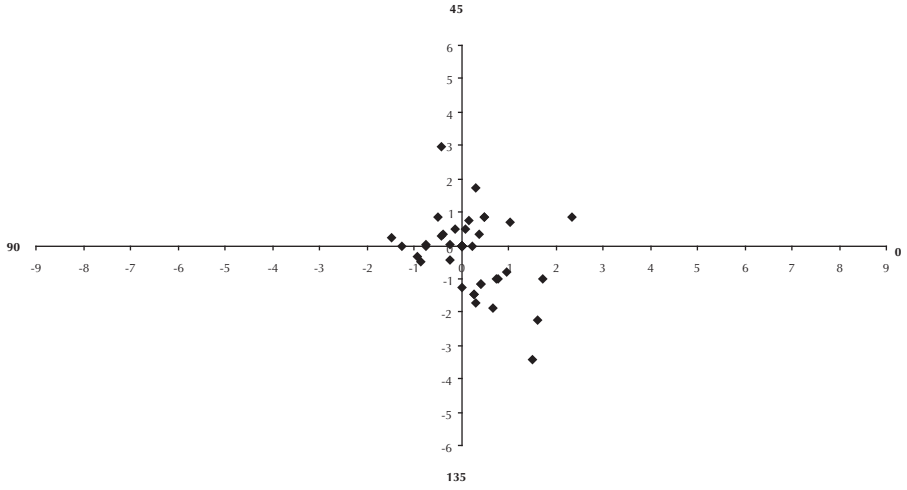

Figure 2. Double-angle minus cylinder plot of postoperative refractive cylinders at 6 months.

an axis of 92.6º. A double-angle minus cylinder power plot of preoperative data is presented in Figure 1. Six months after implantation the astigmatism averaged 0.24 ± 0.85 D at an axis of 150º and one year after implantation the astigmatism averaged 0.20 ± 0.83 D at an axis of 173º. In the double angle minus cylinder power plot for postoperative data at 6 months presented in Figure 2, a tendency towards a clearly lower but more against the rule astigmatism is seen. The average Spherical Equivalent (SE) of the subjective refraction at 6 month follow-up

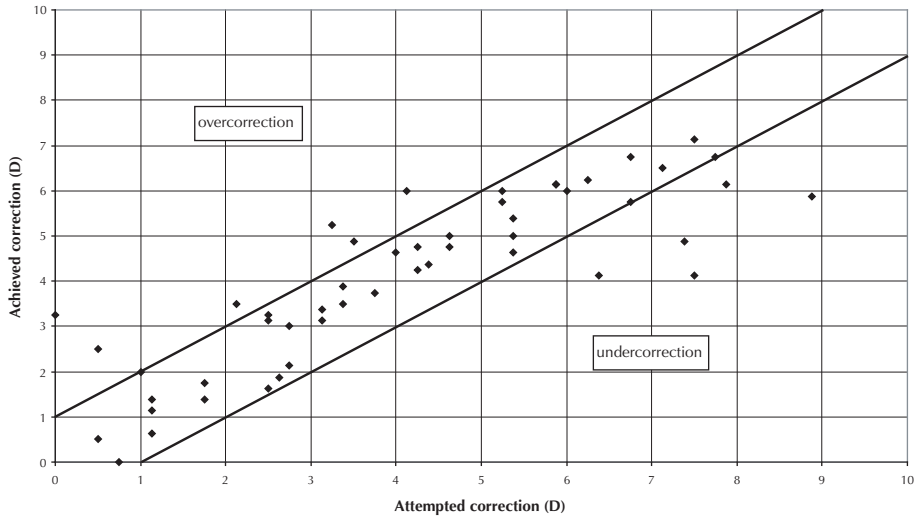

Figure 3. Spread of achieved spherical equivalent refraction at 6 months against intended refraction. D = Diopters.

was –0.125 ± 1.22 D, range -0.25 to 3.00 D and at one year 0.21 ± 1.02 D, range -1.50 to 2.50 D. Six months after surgery 78.0% of the eyes were within ± 1.00 D of emmetropia and 48.0% of the eyes were within ± 0.50 D of emmetropia. The deviation of the achieved SE correction from the attempted SE correction is presented in Figure 3. The safety index after 6 months and 1 year was 1.06 and 1.12 respectively. The efficacy index was 0.82 at 6 months and 0.86 at 1 year. The mean incisionally induced corneal astigmatism was 0.61 ± 0.61 D at a mean axis of 177º.

Intervention was uneventful in all patients. No eyes lost more than two lines in BSCVA at last follow-up. In 3 eyes of 3 patients there was a slight decentration of the TPIOL. However, this did not affect visual acuity. In 2 eyes of 2 patients it was necessary to reposition the lens because of a deviation from the intended axis. In one eye with an implanted cylinder of 3.0 D a deviation of approximately 27º from the intended axis existed, resulting in a residual astigmatism of –2.00 D at an axis of 155º. After the lens position was changed to the correct axis, a residual astigmatism of only -0.50 D at an axis of 163º was left. In the second eye with an implanted cylinder of 7.0 D axis misalignment of approximately 11º resulted in a residual astigmatism of –1.75 D at an axis of 115º. A residual astigmatism of –0.50 D at 40º was left after the lens position was changed.

Iris pigment depositions on the TPIOL were observed in 4 eyes of 3 patients. Two of these patients also reported glare and halo symptoms. Complaints of halo and glare were reported in a total of 4 patients. These 4 patients also comprised

one of the eyes with a loss of 2 lines in BSCVA. No patients reported complaints of binocular diplopia after implantation. IOP after implantation was not significantly different from preoperative IOP. In two eyes a temporary elevation of IOP over 21 mmHg was observed in the first month after operation. A good reaction to topical IOP lowering medication was seen. The mean postoperative endothelial cell count (2976 ± 350 at 6 months and 3000 ± 177 at 1 year) was not significantly different from mean preoperative cell count. No cataract formation was found during follow-up. No posterior synaechiae or fibrin membrane formation was observed in any eye. None of the eyes developed other serious sight-threatening complications such as retinal detachment, or endophthalmitis during follow-up.

DISCUSSION

Refractive surgery encompasses attention to both spherical and cylindrical components of refraction. Especially the treatment of hyperopia combined with astigmatism is challenging. This study demonstrates that in selected patients it is possible to correct moderate to high hyperopia combined with astigmatism by Artisan TPIOL implantation with relatively good refractive results and few complications. Results, however, compare less favourable to myopic toric Artisan implantations.

Artisan TPIOL implantation is a recent alternative to correct ametropia and astigmatism. A few studies report on the results of these TPIOLs.[11-13,16] We have reviewed and summarized the published data for toric Artisan lenses in hyperopic patients. In the European Multicenter Study by Dick et al.[11] 22 hyperopic eyes are included. Preoperative SE refraction was +3.25 D. Average magnitude of refractive astigmatism was 3.70 D (no vector analysis). Mean postoperative endothelial cell count, efficacy index and safety index are given together with the myopic group. All eyes were within ± 1.00 D of the intended refraction. Tehrani and colleagues[13] reported their results in 9 eyes with hyperopia and astigmatism. Mean age in the hyperopic group was somewhat higher with 40 years compared to the myopic group (35 years). Mean preoperative SE refraction was +3.8 D and mean preoperative astigmatism according to vector analysis was 2.9 D. The study reports mainly on the stability of the toric Artisan lens, which was shown to be good. Refractive results are not separately analyzed for the hyperopic group. The last study by Guell et al.[12] included 27 eyes with high myopia or hyperopia and astigmatism. Mean SE refraction was –11.78 D (range: +6.00 to –19.50). The number of hyperopic eyes included is not given

and data are not analyzed separately for myopic or hyperopic eyes. In contrast to the aforementioned studies the present study reports refractive results after toric Artisan lens implantation including a larger group with solely hyperopia and astigmatism (average SE refraction +4.23D) or mixed astigmatism (average SE refraction –1.21D). Hyperopic eyes do not resemble myopic eyes and in our opinion a separate analysis of refractive results is more appropriate. Hyperopic eyes tend to be smaller with smaller anterior segments and a higher frequency of convex irises is seen. Less hyperopic eyes will meet the inclusion criteria for anterior chamber iris-fixated lens implantation compared to myopic eyes. The potential of endothelial cell loss might be higher in hyperopic eyes, because a greater cell loss is reported in eyes with shallower anterior chambers and thicker IOLs.[8,17] In this study we did not observe endothelial cell loss, however, follow-up was only 6 months for all eyes and 1 year for 17 eyes. Longer follow-up is required to assess a potential risk of endothelial cell loss.[17] The serious complication of posterior synaechiae after TPIOL implantation is reported mainly in hyperopic eyes.[8] None of the eyes in this study encountered this problem, probably because of the exclusion of convex irises and anterior chamber depth smaller than 3.00 mm. Since hyperopia becomes an increasing problem with advancing age, patients treated for hyperopia might on average be older than myopic patients. However, patients in our study group were not older than patients implanted with the myopic toric Artisan lens. To uncover any latent hyperopia, cycloplegic refraction in hyperopic patients is important. Hyperopia is more frequently associated with strabismus and amblyopia than myopia. The percentage of eyes with a postoperative UCVA of 20/40 or better is highly affected by the number of amblyopic eyes included. This could account for the lower percentage of UCVA of 20/40 or better found in this study (21 amblyopic eyes) compared to the European multicenter study.[11] In hyperopic and possibly amblyopic eyes the evaluation of efficacy using the UCVA parameter is not very meaningful and the efficacy index might be of more value. Correction of the refractive error with TPIOLs in highly anisometropic patients could exacerbate strabismus or change disparity in retinal image size resulting in diplopic symptoms.[18] Although two patients with the high range astigmatism encountered some trouble in the first few weeks, none encountered permanent problems. In our clinic we test patients with high anisometropia corrected with spectacles by the Awaya aniseiconia test to prevent problems. This is done both with spectacles and with contact lens correction. Tolerance to postoperative induced anisophoria might be predicted by this test. Lens implantation was discouraged in patients who did not tolerate full contact lens correction of their ametropia. In comparison to preoperative visual acuity with glasses in hyperopic

Table 2. Predictability of achieved spherical equivalents after implantation of toric phakic intraocular lenses

Study	Preoperative SE	6 months, refraction within		1 year, refraction within	
		± 0.50 D	± 1.00 D	± 0.50 D	± 1.00 D
Dick et al. [11]	-8.90D	40/48 (83.3%)	48/48 (100%)		
Guell et al.[12]	-11.78D			17/27 (63%)	26/27 (96.2%)
This study	+3.97D	24/50 (48%)	39/50 (78%)	8/17 (47.1%)	14/17 (82.4%)

SE, spherical equivalent

eyes no gain in corrected visual acuity is expected after TPIOL implantation. This is in contrast to myopic eyes where an increase in the size of the retinal image after correction with TPIOL attributes to a gain in visual acuity. This discrepancy can underlie the relatively low safety index found in this study compared to the safety index in myopic patients. In terms of percentages of eyes within ± 1.00 or ± 0.50 D of emmetropia, predictability in this study was lower compared to the correction of myopic astigmatism with Artisan lenses as shown in Table 2. The position of an IOL in a hyperopic eye is more critical than in a myopic eye, since the effect of a miscalculation is inversely related to the length of an eye. Calculation of the dioptric power of the lens with the Van der Heijde formula[14] using anterior chamber depth as a variable might be less accurate in hyperopic eyes.

Accurate axis alignment of the TPIOL is essential for the success, especially in higher astigmatism. Approximately one third of the correction is lost if the lens is rotated 10 degrees off axis. Rotation of the Artisan lens is not likely, because of the firm fixation to the midperipheral iris stroma. Off axis position of an iris-claw lens is most likely caused by incorrect placement of the lens in the axis during surgery. Lens position had to be changed in two eyes of two different patients in our study. The technique to change the lens position is relatively simple. The iris is pushed back through the slits of the haptic and the lens is refixated to the iris at a different part. After the lens position in two patients was changed, astigmatism reduced to –0.50 D in both eyes compared to –2.00 D and –1.75 D before.

Alternative surgical options for the correction of hyperopia with astigmatism have their limits. Large treatment zones are necessary to correct astigmatism and hyperopia with LASIK or PRK. Hyperopic PRK appears to be relatively safe and effective for corrections up to + 4.00 D.[3,19] In higher corrections reduced predictability and possible loss of best spectacle corrected visual acuity are reported.[20] After treatment of hyperopic astigmatism with PRK a higher percentage of eyes (15.8%) is reported to lose two or more lines BSCVA.[5] In this study we observed that only 4% of the eyes lost two or more lines at six months.

The higher risk of haze or scar formation with PRK in larger hyperopia might underlie this difference. Significant regression has been reported in LASIK for hyperopia, being strongly associated with the magnitude of hyperopia.[20] In comparison to hyperopic PRK and LASIK, hyperopic TPIOL implantation is expected to achieve an earlier and more stable refraction. It is difficult to compare the results of our study with the results of studies on the treatment of hyperopia and astigmatism with either LASIK or PRK, mainly because of a large variation in the range of preoperative hyperopia. LASIK has been shown to be very effective and predictable in lower hyperopia up to 3 D.[1] However, above approximately 4-5 D, efficacy and stability falls off markedly.[21,22] Spherical ametropia and the amount of cylinder was rather high in this study with only 9 eyes having either a SE below 3 D or a cylinder lower than 4 D. Many patients included in this study were referred to us from other centres to evaluate the possibilities for Artisan lens implantation, because LASIK or PRK was not an option. Posterior toric IOL implantation after clear lens extraction is another option for the correction of high astigmatism and hyperopia. Clear lens extraction, however, will result in permanent and complete loss of accommodation in relatively young patients. Furthermore, a greater incidence of intraoperative complications and postoperative retinal detachment is reported and rotational stability might be a problem with toric IOLs in the capsular bag.[23] Other phakic IOL options are posterior chamber (PC)IOLs.[9,10,24] The advantage of a phakic PCIOL lens in hyperopic patients might be a greater distance between the IOL and the endothelial layer. However, other risks are reported in these PCIOLs such as cataractogenesis and pigment dispersion.[9,25-28] In hyperopic eyes there might be a significantly higher risk of developing a pupil block glaucoma.[24] Besides, until now phakic toric PCIOLs for the correction of both hyperopia and astigmatism in a single procedure have not been commercially available.

The Artisan hyperopic TPIOL might be a valuable alternative to correct combined hyperopia and astigmatism in carefully selected patients with clear lenses and an anterior chamber depth of at least 3.00 mm and no convex irises. More patients should be studied to assess whether the used formula for lens calculation have to be adjusted for hyperopic eyes, since the refractive outcome appears to be less accurate as compared to the implantation with the myopic toric Artisan lens. Furthermore, a larger follow-up is needed to evaluate the long-term effect of TPIOL on endothelial cell loss.

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CHAPTER 9

SUMMARY AND CONCLUSIONS

SAMENVATTING IN HET NEDERLANDS

WAYS TO IMPROVE VISUAL OUTCOME IN CORNEAL TRANSPLANTATION, CORNEAL PATHOLOGY AND ASTIGMATISM

The normally transparent cornea can lose its ability to refract light regularly from various conditions. Among these conditions are corneal opacities and corneal diseases leading to a distortion of the corneal contour. Vision might be restored by a corneal transplantation. Corneal transplantation is widely practised and can be very successful. The high success rate of corneal transplantation has been attributed to the avascularity of the cornea and the immune privileged site of the cornea. The leading cause, however, of corneal graft failure is graft rejection. The incidence of graft rejection and failure is increased in high-risk patients having corneal vascularisation or a history of previous graft rejection. For a patient to benefit from corneal transplantation the graft must be optically clear with minimal aberrations. Consequently, reducing corneal graft failure and reducing postoperative astigmatism can improve the outcome of a corneal transplantation. The aim of studies described in this thesis was to improve the (visual) outcome of corneal transplantations. The ultimate life span of each corneal graft is limited, even if an immune reaction has never occurred. In an attempt to postpone a corneal graft we investigated the toric Artisan lens as an alternative to correct high astigmatism associated with keratoconus and marginal degeneration. The toric Artisan lens was also investigated in eyes without corneal pathology.

Chapter 1 is a short introduction to this thesis, with a review of the literature on the immunologic mechanisms associated with corneal transplantation in the first part and a review of published studies on refractive surgery in the second part.

The objective of the study described in **Chapter 2** was to assess the contribution of coincidental HLA matches between donors and recipients to rejection free graft survival. All donor corneas were randomly allocated. Retrospective HLA-A, HLA-B and HLA-DR typing on corneal derived DNA samples from recipients and donors was performed on cases with and cases without graft rejection. Coincidental HLA matches were observed. This finding could be explained by the abundance of certain HLA alleles in a rather homogeneous gene pool from which both donors and recipients are derived. The conclusion of this study was that coincidental HLA-A and HLA-DR matches were associated with a prolonged rejection free survival time in the total group and in the high-risk group, respectively. This result supports the beneficial effect of prospective HLA-A and HLA-DR typing upon corneal graft survival.

Chapter 3 deals also with the role of HLA matching on corneal graft rejection**.** The study population described in this study consisted of high-risk patients who

received a matched corneal transplant. Allocation of donor corneas was based on the acceptation of a minimum of 2 HLA-A and HLA-B antigen matches based on broad typing. Retrospective analysis of HLA antigens on the more selective split typing level was also performed. The influence on immunologic graft failure for an increasing number of matched HLA-A and HLA-B antigens based on split typing was analysed. Rejection was the cause of one third of all graft failures. Having fewer HLA-A and HLA-B antigen split mismatches (0 or 1 mismatch) was in a multivariate analysis associated with a longer immune failure free graft survival and with a better overall graft survival.

In **Chapter 4** we describe the results of a study comparing two suture materials used for penetrating keratoplasty in patients with Fuchs' endothelial dystrophy. A group of transplants sutured with Nylon filament was compared to a group of transplants sutured with Mersilene filament. Complications related to suture material and astigmatism control were investigated. Nylon is commonly used in penetrating keratoplasty, however, it may loosen and weaken over time, due to biodegradation. Biodegradation is not seen in Mersilene sutures. Although transplant survival did not differ between groups, astigmatism and risk of developing certain complications appeared to be higher in the Mersilene group. Transplants sutured with Mersilene had a significantly higher risk of surgical intervention to correct astigmatism or wound dehiscence. Longer follow-up after which all Nylon sutures are removed is needed to draw strong conclusions because the long lasting tensile strength of Mersilene may lead to fewer complications and less wound dehiscence with subsequent astigmatism in long-term follow-up.

Chapter 5 and **Chapter 6** report on the results of phakic toric Artisan lens implantation in patients with keratoconus and marginal degeneration. This procedure was investigated as an alternative for keratoplasty. All patients included in these studies were contact lens intolerant and had a clear central cornea. After IOL implantation patients were highly satisfied with the refractive results. Spectacles to correct the residual refractive error were well-tolerated by all patients. A penetrating keratoplasty for the correction of astigmatism associated with keratoconus and marginal degeneration could be delayed or even avoided in these patients. Especially for patients with associated myopia, toric Artisan lens implantation could be beneficial even in case the full corneal astigmatism cannot be treated.

Chapter 7 and **Chapter 8** deal with the safety, efficacy and predictability of phakic toric Artisan lens implantations in patients with astigmatism and myopia or hyperopia. Proper surgical axis alignment of the toric IOL is crucial to the success of this treatment. In Chapter 7 the method of marking the enclavation site using the Javal keratometer was evaluated. With the use of Javal keratometer

marking, axis misalignment of the IOL appeared to be a minor disturbing factor for predictability in the myopic population. Insicionally induced astigmatism, however, contributed to an overcorrection of the achieved cylinder. A systematic undercorrection of –0.50 Diopters for attempted cylindrical outcome is advised to achieve a refractive result closer to emmetropia. Although refractive results were rather good in terms of efficacy and safety, the predictability for eyes with astigmatism and hyperopia appeared to be lower in comparison with eyes with astigmatism and myopia.

The clinical relevance of studies described in this thesis is multifold. Our data from the studies described in chapter 2 and 3, together with those of others suggest that all corneal transplant patients, high-risk and low-risk, could benefit from various degrees of HLA-matching. As a consequence of the results of these positive matching studies an increase in demand for matched corneal grafts is to be expected. In my opinion HLA matching is one way to improve efficiently graft survival. Several points should be considered when attempting to match donor and recipient. It is both more laborious and more expensive. The HLA system is polymorphic and the probability of finding a complete match is low. The chance of a good match on the more selective split antigen level is even lower than on the broad antigen level. Subsequently, allocation based on (split) HLA matching will have consequences for the time that a patient will have to wait for a transplant. Time spent on the waiting list is associated with a reduced quality of life and possibly with social costs of blindness. One should be aware of the fact that the benefit of HLA matching shown in chapter 2 and 3 regards only patient groups. The individual patient may not benefit from HLA matching. If the lifespan of a transplant is expanded by a good match, younger high-risk patients are expected to benefit the most. In future research the potential economic effects and increased waiting time associated with the transplantation of donor corneas with various numbers of HLA mismatches should be weight against the possible benefits.

Also without immune rejection the functional outcome of a corneal transplant could be reduced by high astigmatism. High astigmatism after transplantation is still a major complication that remains to be solved. It appears that Mersilene sutures will not solve this problem. In eyes with endothelial disorders, astigmatism after transplantation might be better controlled with new or rediscovered techniques such as posterior lamellar keratoplasty and mushroom shaped keratoplasty. In future research these techniques should be compared with conventional penetrating keratoplasty. Points of interest are endothelial cell count (related to transplant survival) and visual outcome (related to astigmatism).

The phakic toric IOL can correct astigmatism and ametropia associated with corneal pathology but is never a treatment of the underlying disorder in contrast to penetrating keratoplasty. Progression of the disease can negatively influence refractive outcome after IOL implantation. The purpose of phakic toric IOL implantation is to postpone keratoplasty. Taking into account the results of our studies, we consider the phakic toric Artisan lens a suitable option to correct high myopia and astigmatism in select patients with keratoconus and marginal degeneration. As is shown by our case report, it might not be necessary to correct the full refractive cylinder. If the power of the cylinder of the IOL is calculated with the currently used formula based on Plano attempted refraction, an overcorrection of the cylinder might be the result. To enhance predictability, the results of toric phakic IOL implantation should be investigated in more patients with keratoconus and marginal degeneration.

Refractive surgery represents a new and fast evolving field. Current refractive surgery techniques include intraocular procedures and methods that alter the cornea. To discuss the possibilities with a patient, an accurate analysis of refractive results and complications of different treatment techniques is required. The best treatment option depends on several variables and differs for each individual patient. A possible long-term complication after phakic Artisan lens implantation is endothelial cell loss, which might be more pronounced in hyperopic eyes. Longer follow-up than provided by our studies is required to assess the potential risk of endothelial cell loss.

Proper patient selection for each refractive surgery procedure is crucial to achieve efficient and safe results. The results of our studies on the Artisan lens could be used to inform patients. Furthermore, the analysis of different variables contributing to the final refractive result could increase the predictability of toric phakic IOL implantation.

SAMENVATTING IN HET NEDERLANDS

MOGELIJKHEDEN OM HET (VISUELE) RESULTAAT TE VERBETEREN BIJ CORNEATRANSPLANTATIES, CORNEAPATHOLOGIE EN ASTIGMATISME

Het gezonde hoornvlies (cornea) is een heldere structuur en draagt door zijn specifieke vorm bij aan de breking van licht. Diverse aandoeningen kunnen de helderheid of de vorm van het hoornvlies verstoren, hetgeen kan leiden tot een verminderd gezichtsvermogen. Om het gezichtsvermogen te herstellen kan een hoornvliestransplantatie nodig zijn. Hoornvliestransplantaties behoren wereldwijd tot de meest frequent uitgevoerde transplantaties en worden gekenmerkt door een relatief hoog succespercentage. In tegenstelling tot andere orgaantransplantaten, kunnen hoornvliestransplantaten overleven zonder gebruik van systemische medicatie. Dit fenomeen wordt onder meer toegeschreven aan de avasculariteit van het hoornvlies en de speciale positie van het hoornvlies ten opzichte van het afweersysteem. Desondanks is een afstotingsreactie de belangrijkste oorzaak voor het troebel worden van het transplantaat. Risicofactoren hiervoor zijn vaatingroei en afstoting van een eerder transplantaat. Astigmatisme is naast falen van het transplantaat een belangrijke postoperatieve complicatie, die tot een slecht visueel resultaat kan leiden ondanks een helder transplantaat. Door cilindrisch geslepen brillenglazen kan regulair astigmatisme gecorrigeerd worden. Behalve een zeer belangrijke postoperatieve complicatie kan het astigmatisme ook de indicatie voor een hoornvliestransplantatie zijn, zoals bijvoorbeeld bij keratoconus en marginale degeneratie. Het succes van een hoornvliestransplantatie kan worden verbeterd door falen te voorkomen en astigmatisme na de operatie te reduceren. Echter, zelfs als er geen afstoting is geweest, is de overleving op de lange duur beperkt. In dit proefschrift worden onderzoeken beschreven naar factoren die het risico van afstoting verlagen en het optreden van postoperatief astigmatisme reduceren. Ook is gekeken naar de toepasbaarheid van de torische Artisan lens als alternatief voor een hoornvliestransplantatie bij een subpopulatie van relatief jonge patiënten. Deze patiënten hadden vanwege astigmatisme bij een keratoconus of marginale degeneratie een indicatie voor een hoornvliestransplantatie. Tenslotte onderzochten wij de veiligheid en effectiviteit van torische Artisan lenzen in ogen zonder hoornvliespathologie.

Hoofdstuk 1 is een korte introductie met een overzicht van de literatuur over transplantaat afstotingen in het eerste deel en een overzicht van refractiechirurgische behandelingen in het tweede deel.

In **Hoofdstuk 2** wordt een studie beschreven waarin retrospectief gekeken is of toevallig aanwezige overeenkomsten in hoornvliesweefsel van donor en ontvanger resulteren in een kleinere kans op afstoting. De weefselantigenen van donor en patiënt waren niet bekend ten tijde van transplantatie. Tijdens de operatie werd van zowel patiënt als donor hoornvliesweefsel bewaard. Achteraf werd uit dit weefsel DNA geïsoleerd. Uit het DNA werden met moleculair biologische technieken de HLA-A, HLA-B en HLA-DR weefseltyperingen bepaald. Patiënten met 1 of 2 HLA-A overeenkomsten met de donor hadden een significant langere overleving van het transplantaat zonder afstotingsreactie dan patiënten zonder HLA-A overeenkomsten. Bij patiënten met vooraf een verhoogd risico op falen van het transplantaat, resulteerden overeenkomsten in HLA-DR in een langer afstotingsvrij interval van het transplantaat. De conclusies van deze studie zijn dat toevallig aanwezige overeenkomsten in weefseltypen tussen donor en ontvanger bijdragen aan een langer afstotingsvrij interval en dat er een positief effect op de transplantaatoverleving te verwachten is indien de donor geselecteerd wordt op basis van overeenkomsten in HLA-A en HLA-DR.

Hoofdstuk 3 gaat eveneens over de rol van overeenkomsten in weefselantigenen bij hoornvliestransplantaties. De studiepopulatie bestond uit patiënten met een verhoogd risico op falen van het transplantaat. Alle patiënten kregen een donorhoornvlies met tenminste twee overeenkomsten in HLA-A en HLA-B op basis van een zogenaamde 'broad' typering. In retrospectie werd gekeken naar het effect op afstoting van overeenkomsten in HLA-A en HLA-B op basis van een verfijndere indeling, de zogenaamde 'split' typering. Alleen afstotingen die leidden tot een falen van het transplantaat werden geanalyseerd. Afstoting was een belangrijke oorzaak voor het falen, namelijk bij 1/3 van alle transplantaten die faalden was een afstoting hiervoor de reden. Het bleek dat transplantaten die een betere overeenkomst hadden op basis van de 'split' typering een beduidend lager risico hadden op falen door een afstoting. Bovendien was de algehele overlevingsduur van het transplantaat langer voor de transplantaten met een hogere mate van overeenkomst. De conclusie van deze studie is dat het toewijzen van donorhoornvliezen op basis van geen of slechts één afwijking bij split typering van HLA-A en HLA-B kan bijdragen aan een betere transplantaat overleving.

In **Hoofdstuk 4** worden twee hechtmaterialen voor hoornvliestransplantaties met elkaar vergeleken voor wat betreft de bijwerkingen van het materiaal en het induceren van postoperatief astigmatisme. Nylon is het meest gebruikte

hechtmateriaal. Het nadeel van Nylon is dat het na verloop van tijd trekkracht verliest en uiteindelijk oplost. Een mogelijk voordeel van het veel minder gebruikte Mersileen is dat het de trekkracht behoudt omdat het niet degradeert. De studiepopulatie bestond uit patiënten die een hoornvliestransplantatie kregen vanwege Fuchse dystrofie en was onderverdeeld in een Nylon groep en een Mersileen groep. Er was geen verschil in transplantaat overlevingsduur tussen de groepen. Het astigmatisme was gedurende de eerste twee jaar na transplantatie duidelijk lager in de Nylon groep. In de Mersileen groep was de kans op bepaalde bijwerkingen (het optreden van een infiltraat, littekenvorming langs de hechting en het insnijden van de hechting) groter. Bovendien was in de Mersileen groep eerder een aanvullende operatie nodig om het transplantaat in niveau te krijgen of om astigmatisme te corrigeren. Het lijkt echter of bijwerkingen door loslating van de hechtingen na twee jaar vaker voorkomen bij de Nylongroep. Daar deze bijwerkingen ernstig kunnen zijn en zelfs tot blindheid of verlies van het oog kunnen leiden, bestaat er wellicht op de lange termijn een voordeel voor de transplantaten ingehecht met Mersileen.

In **Hoofdstuk 5 en 6** worden patiënten beschreven met een zeer hoog astigmatisme als gevolg van keratoconus en marginale degeneratie. Bij deze groep patiënten is gewoonlijk een hoornvliestransplantatie geïndiceerd indien zij ondanks correctie met bril of contactlenzen niet meer goed kunnen zien. Wij onderzochten de toepasbaarheid van de torische Artisan lens als alternatief voor een hoornvliestransplantatie. Dit type lens wordt in de voorste oogkamer aan de iris vastgeklemd en bevat zowel een sferische als een cilindrische correctie. De resultaten van implantatie van de lens in 8 ogen met hoornvliespathologie toonden aan dat de best mogelijk gezichtsscherpte verbeterde en dat een transplantatie uitgesteld dan wel voorkomen kon worden. Alle patiënten verdroegen de bril voor correctie van het resterende astigmatisme goed en waren zeer tevreden over het resultaat van de behandeling.

Indien de torische Artisan lens gebruikt wordt in ogen zonder hoornvliespathologie met het doel zowel de sferische als de cilindrische afwijking te verminderen, is er sprake van refractiechirurgie. Veelal wordt de Artisan lens gebruikt indien de refractieafwijking zodanig is dat een persoon niet voor een laserbehandeling in aanmerking komt. Om de Artisan lens in het oog te plaatsen is een operatie nodig, waarbij er een opening van 5,5 mm wordt gemaakt. In **Hoofdstuk 7 en 8** onderzochten wij de veiligheid, effectiviteit en voorspelbaarheid van Artisan lens implantaties in ogen zonder andere bekende afwijkingen. Tevens werd nagegaan wat de invloed was van de plaats van de lens in het oog en de opening van 5,5 mm op het uiteindelijke resultaat. In Hoofdstuk 7 zijn patiënten beschreven die vooraf bijziend waren en in Hoofdstuk 8 patiënten

die vooraf verziend waren. Bij beide groepen bleek de veiligheid hoog. De effectiviteit, veiligheid en voorspelbaarheid van de behandeling waren goed. De voorspelbaarheid van de resultaten voor de groep van bijziende patiënten was beter dan voor de groep van verziende patiënten. Wij berekenden dat de 5,5 mm opening bijdraagt aan een kleine overcorrectie van de cilinder.

Het belang van de studies beschreven in dit proefschrift is meervoudig. De bevindingen in hoofdstuk 2 en 3 tezamen met resultaten van andere recente studies, suggereren dat hoornvliestransplantatiepatiënten gebaat kunnen zijn bij een bepaalde mate van overeenkomst in HLA antigenen. Deze bevindingen kunnen aanleiding geven tot het vaker aanvragen van een zogenaamd gematched donorhoornvlies. Aan de allocatie van donorhoornvliezen op basis van HLA overeenkomsten met de patiënt zijn echter ook nadelen verbonden. Behalve dat een dergelijk allocatie systeem duurder kan zijn en logistieke problemen met zich meebrengt, kan een patiënt hierbij langer op een donorhoornvlies moeten wachten. Een langere wachttijd is geassocieerd met een verminderde kwaliteit van leven en mogelijk ook met extra kosten ten gevolge van een langere periode van slechtziendheid. Voor de individuele patiënt hoeft het geen voordeel te zijn een donortransplantaat met HLA overeenkomsten toegewezen te krijgen. Zo is een oudere patiënt met een laag risico op afstoting van het transplantaat meer gebaat bij een snelle transplantatie dan bij een hogere lange termijn overlevingskans van het transplantaat. In toekomstig onderzoek zullen van een allocatie systeem gebaseerd op HLA overeenkomsten de economische effecten en de implicaties voor de wachttijd moeten worden onderzocht.

Een helder transplantaat kan ook zonder dat het een afstoting heeft doorgemaakt door een hoog astigmatisme een slecht functioneel resultaat geven. Om een betere gezichtsscherpte te bereiken na transplantatie wordt een zo laag mogelijk astigmatisme nagestreefd. Hoog astigmatisme is echter nog steeds een belangrijk probleem na transplantatie. Mersileen hechtingen lijken op de korte termijn geen oplossing voor dit probleem te zijn. Nieuwe (posterieure lamellaire transplantaten) en herontdekte (paddestoelvormige transplantaten) technieken kunnen misschien het astigmatisme adequater reduceren.

De resultaten van de studies in hoofdstuk 5 en 6 tonen aan dat de implantatie van een torische lens in het oog bij een selecte patiëntengroep een hoornvliestransplantatie kan uitstellen, hetgeen met name voor jonge patiënten gunstig kan zijn omdat de overleving van een hoornvliestransplantaat uiteindelijk gelimiteerd is. Het plaatsen van de lens in het oog is echter geen behandeling voor de onderliggende aandoening en voorkomt progressie van de aandoening niet. Om de voorspelbaarheid van de correctie met de Artisan lens in patiënten

met keratoconus en marginale degeneratie te verbeteren, zullen de gegevens van meer patiënten die deze procedure hebben ondergaan moeten worden geanalyseerd. Eventueel kan dan de gebruikelijke formule voor het berekenen van de lenssterkte worden aangepast.

De refractiechirurgie is een jong en een snel ontwikkelend vakgebied binnen de oogheelkunde. Refractiechirurgische behandelingen kunnen in twee groepen worden ingedeeld: een groep waarbij het hoornvlies wordt veranderd en een groep waarbij er een operatie in het oog plaatsvindt. Individueel zal moeten worden afgewogen welke behandeling het beste is. Goede analyse van alle mogelijke refractiechirurgische behandelingen is essentieel om kandidaten voor refractiechirurgie goed te kunnen informeren en adviseren. Wij denken dat de laatste twee studies hier zeker een bijdrage aan leveren.

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