Biocompatibility of Ferrara intracorneal ring segment with and without chondroitin sulfate coating. Clinical and histopathological evaluation in rabbits[1]

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ABSTRACT

PURPOSE: To investigate and compare the biocompatibility of two types of Ferrara intracorneal ring segment: with and without chondroitin sulfate coating by clinical and histopathological evaluation.

METHODS: A randomized experimental study was carried out on thirty right-eye corneas from 30 Norfolk albino rabbits allocated into two experimental groups: Group G1 – implanted with Ferrara intracorneal ring segment without coating (FICRS) and Group G2 – implanted with Ferrara intracorneal ring segment with chondroitin sulfate coating (FICRS-CS). Left eyes formed the control group. Clinical parameters analyzed were: presence of edema, vascularization, infection and ring extrusion one, 30, and 60 days after surgery. Histopathological parameters analyzed were: number of corneal epithelial layers over and adjacent to the ring, presence of spongiosis, hydropic degeneration, basement membrane thinning, inflammatory cells, neovascularization and pseudocapsule formation.

RESULTS: At clinical examination 60 days after implant, edema, vascularization and extrusion were observed respectively in 20%, 26.7%, 6.7% of FICRS corneas and in 6.7%, 6.7%, and 0% of FICRS-CS corneas. Histopathological evaluation showed epithelial-layer reduction from 5 (5;6) to 3 (3;3) with FICRS and from 5 (5;5) to 4 (3;5) with FICRS-CS in the region over the ring. Epithelial spongiosis, hydropic degeneration, and basement membrane thinning were present in 69.2%, 53.8%, and 69.2% of FICRS and in 73.3%, 73.3%, and 46.7% with FICRS-CS, respectively. Vascularization was present in 38.5% of FICRS and 13.3% with FICRS-CS, inflammatory cells in 75% of FICRS and 33.3% with FICRS-CS, and pseudocapsule in 66.7% of FICRS and 93.3% with FICRS-CS. Giant cells occurred only in the FICRS-CS group (20%).

CONCLUSION: Ferrara intracorneal rings coated with chondroitin sulfate (FICRS-CS) caused lower frequency of clinical and histopathological alterations than Ferrara intracorneal rings without the coating (FICRS), demonstrating higher biocompatibility of the FICRS-CS.

Key words: Prosthesis Implantation. Corneal Neovascularization. Chondroitin Sulfates. Cornea. Rabbits

Introduction

Highly irregular astigmatism caused by diseases that deform the cornea preclude vision correction with the available optical resources. Keratoconus, laser-assisted *in situ* keratomileusis (LASIK), and penetrating or laminar keratoplasty are some of the main causes of corneal deformity[1-3].

Keratoconus is a generally bilateral non-inflammatory progressive corneal ectasia that occurs in all races. Its prevalence is approximately 3.34% in first generation relatives and varies from 0.05% to 0.23% in the general population[4]. The disease begins in puberty and the refractive error is generally corrected with hard contact lenses, but 21.6% to 44% of cases require penetrating keratoplasty to restore vision[5]. Intracorneal rings are an alternative to delay potentially aggressive keratoplasty, or in patients intolerant to contact lens[6].

Iatrogenic corneal ectasia is the most feared post-LASIK complication, yet little is known about its incidence and prevalence. Pallikaris *et al*.[7] reported this complication in 0.66% of eyes submitted to LASIK in a study involving 2873 patients submitted to the procedure between May 1995 and November 1999. LASIK is performed in many countries. In the USA, the estimated 8 million persons who have been submitted to LASIK could potentially lead to a large number of iatrogenic ectasias[8].

Corneal transplants are performed all over the world. APABO[9] estimates that in 2004 there were 8400 cornea transplants in Brazil and 46841 in the USA, whereas the post-transplant incidence of high degree astigmatism varied from 10% to 20%[10,11].

In the last 20 years, studies of intracorneal ring implants have shown promising evolution in relation to corneal ectasia stabilization, corneal apex regularization, improvement in contact lens adaptation, and improved visual acuity in keratoconus and post-LASIK corneal ectasia as well as in post-transplant astigmatism[12-14]. More recently the association of such implants with corneal cross-linking has shown good results[15].

Implants of polymethylmethacrylate (PMMA) rings have been described as a simple, reversible, easy-to-learn method suitable for outpatients which allows the normal cornea structure to be preserved without removing corneal tissue or causing corneal reaction[16,17]. However, cases of corneal extrusion and infection have been reported for varying periods after this type of implant[18,19] and may be related to corneal incompatibility with PMMA.

The types of intracorneal ring segments available globally are all made of PMMA (Intacs®, Intacs-SK®, Ferrara Ring®, Keraring®, and Cornealring®) varying only in diameter, cross-section, arc length, thickness, and the internal and external curvature radii[20].

Glycosaminoglycans such as chondroitin sulfate are found in the extracellular corneal matrix and actively participate in the corneal homeostatic process[21]. Therefore coating the PMMA intracorneal rings with chondroitin sulfate may improve biocompatibility and reduce complications such as corneal extrusion and infection. No studies were found that have compared alterations and complications caused by intracorneal rings coated with chondroitin sulfate (FICRS-CS) versus those commercially available without the coating (FICRS).

The aim of the study was to investigate and to compare the biocompatibility of two types of Ferrara intracorneal ring segment: with and without chondroitin sulfate coating by clinical and histopathological evaluation.

Methods

The study was approved by the Ethics Committee on Animal Research, Botucatu Medical School - UNESP, number 502-05.

A randomized experimental study was performed on 30 healthy female Norfolk albino rabbits weighing from 1550g to 2650g, with normal eyes at clinical examination. The animals were supplied by the Botucatu School of Medicine's Central Animal Colony.

The rabbits were randomly divided into two groups. Group 1 (n=15) was implanted with a PMMA Ferrara intracorneal ring segment without chondroitin sulfate coating (FICRS) in the right eye cornea (RE). Group 2 (n=15) was implanted with a PMMA Ferrara intracorneal ring segment with chondroitin sulfate coating (FICRS-CS) in the right-eye cornea (RE). Left-eye corneas (LE) formed the control group.

The only difference between the Ferrara intracorneal ring segments was the presence of chondroitin sulfate coating in the FICRS-CS and its absence in the FICRS. Intracorneal ring segment dimensions were: 125 micron thickness, 150° arc length, 5mm apex diameter, one orifice at each extremity, and a constant triangular section base of 600µm.

All ring segments were implanted by one of the authors (EA) after intravenous anesthesia with 4% sodium pentobarbital (1ml/Kg) and topical anesthesia with 1% tetracaine hydrochloride. The protocol for intracorneal ring implant surgery was as follows: asepsis, placement of a Barraquer blepharostat, marking the anatomical center of the cornea with a Sinsky hook, marking optical zones at 3, 5, and 7mm from the center mark with an optical zone marker (Storz E 9032), making of a 1.2mm radial

incision at 12 o'clock between the 5 and 7mm optical zones with a diamond knife - double cut (Storz E-9055 TAA) to 80% of the corneal thickness, evaluated by ultrasonic pachymetry (Alcon® pachymeter - 8065973401 Serial Nº 3779), introducing a Soares spreader to start the tunnel, followed by a semicircular Ferrara tunnel marker which was rotated 180º counterclockwise, and positioning of the PMMA intracorneal ring with or without the coating according to the group. The radial incision was not sutured.

After surgery, 0.3% ofloxacin eye drops (Oflox 0.3% Allergan®) were applied to the right eye every eight hours for 15 days.

The following clinical parameters were evaluated with the aid of a surgical microscope: presence of edema, presence of vascularization, presence of infection and ring extrusion. These parameters were evaluated at three different moments: M1 - 1 day, M2 - 30 days, and M3 - 60 days after implant.

After M3, animals were euthanized with a lethal dose of pentobarbital and the eyes enucleated. The corneas were removed and bisected through the middle of the ring in the RE (3 o'clock to 9 o'clock section). One of the halves was fixed in 10% buffered formaldehyde whereas the other was sent for scanning electron microscopy which is not covered in this study. Laminas were prepared and stained with hematoxylin eosin and with periodic acid of Schiff. Histological analysis was performed on two different regions of the cornea: over the ring and adjacent (lateral, at 7mm optical zone) to the ring in RE. In control eyes, analyzed regions corresponded to the optical zones from 3 to 5mm. In both zones the analysis included: epithelium, stroma, Descemet membrane and endothelium. Histopathological analysis was performed masked.

The epithelium was evaluated for number of layers, presence of spongiosis, presence of hydropic degeneration, and presence of thinning in the basement membrane. The stroma was evaluated for the presence of neovascularization, inflammatory cells and pseudocapsule.

Statistical analysis was performed using SPSS Version 15 using the parametric paired Student's *t* and Mann-Whitney tests and the non-parametric Wilcoxon test for dependent samples. Comparisons of proportions were performed by Chi-squared test or Fisher's Exact Test and comparisons for the same individual with MacNemar test. A 5% significance level was adopted ($p<0.05$).

Results

Clinical parameters

Edema was observed at all three moments in G1 and at two moments in G2. The edema frequencies in M1 were 66.7% and 93.3% respectively for G1 and G2. At M2 edema was observed only in G1 at the frequency of 13.3%. At M3, edema occurred in 20% of G1 and in 6.7% of G2. The difference was not statistically significant (Table 1).

Corneal vascularization occurred only at M3, at lower frequency in G2 but without significant statistical difference (Table 1). Ring extrusion was only observed in G1 (6.7%) (Table 1). Infection was not present in any corneas.

TABLE 1 - Presence of edema, vascularization, and ring extrusion in number (n) and percentage (%) in right eyes (RE) implanted with intracorneal rings, and in left-eye (LE) controls without implant.

			G1 (FICRS)		G2 (FICRS-CS)		P
			N	%	n	%	
Edema	M1	RE	10	66.7	14	93.3	0.169
		LE	-	-	-	-	-
	M2	RE	2	13.3	-	-	0.483
		LE	-	-	-	-	-
	M3	RE	3	20	1	6.7	0.598
		LE	-	-	-	-	-
Vascularization	M1	RE	-	-	-	-	-
		LE	-	-	-	-	-
	M2	RE	-	-	-	-	-
		LE	-	-	-	-	-
	M3	RE	4	26.7	1	6.7	0.142
		LE	-	-	-	-	-
Extrusion	M1	RE	-	-	-	-	-
		LE	-	-	-	-	-
	M2	RE	1	6.7	-	-	1
		LE	-	-	-	-	-
	M3	RE	-	-	-	-	-
		LE	-	-	-	-	-

M1: Day 1 after surgery
M2: Day 30 after surgery
M3: Day 60 after surgery
G1: Group 1 - intracorneal ring implant without coating (FICRS)
G2: Group 2 - intracorneal ring implant with chondroitin sulfate coating (FICRS-CS)
Fisher's Exact test

Morphological parameters

Control group corneas (LE) presented an epithelium

formed by 5-6 layers of cells, having one line of elongated columnar basal cells, two layers of polygonal cells, two or three layers of wing cells, and one layer of squamous cells. The basement membrane (BM) showed homogenous thickness (Figure 1).

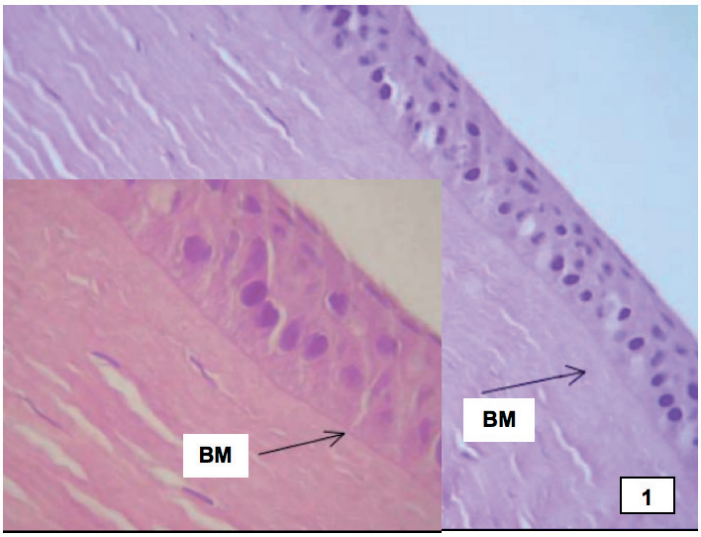

FIGURE 1 - Rabbit corneal epithelium layers and homogenous thickness BM from control left eyes. Hematoxylin-eosin stain, HE x200 and detail HE x1000.

In the region over the ring a diminution was observed in the number of epithelial cell layers, in both experimental groups. The reduction was seen mainly in the middle third, which is formed by wing cells (Figure 2).

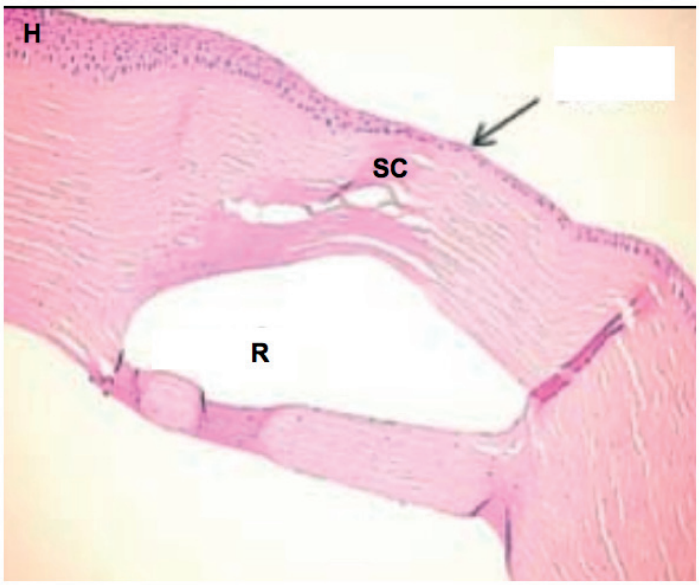

FIGURE 2 - Rabbit cornea from G1. Ring space (**R**). Observe the accentuated thinning of the epithelial cell layers (arrow) and intense stromal compaction (**SC**) in the region over the intracorneal implant, H (Hypertrophy of the epithelium), HE x100.

The median number of layers was five (5;6) in control eyes and three (3;3) and four (3;5) respectively in G1 and G2, but the reduction was significant only in G1 (Table 2).

TABLE 2 - Median number of epithelial cell layers from rabbit corneas with intracorneal ring implants in right eyes (RE), in the regions over and adjacent to the ring, and in the left eye (LE) controls.

		RE (With ring implant)	LE (Control)	P
Over	G1 (FICRS) (n=13)	3 (3;3)	5 (5;6)	0.001
	G2 (FICRS-CS) (n=15)	4 (3;5)	5 (5;5)	0.670
		0.061	0.488	
Adjacent	G1 (FICRS) (n=13)	6 (5;6)	5 (5;6)	0.245
	G2 (FICRS-CS) (n=15)	5 (4;7)	5 (5;5)	0.670
		0.386	0.309	

G1: Group 1 - intracorneal ring implant without coating (FICRS)
G2: Group 2 - intracorneal ring implant with chondroitin sulfate coating (FICRS-CS)
Mann-Whitney to compare groups at each moment
Wilcoxon to compare eyes in each group
Note: Analysis in G1 was performed on 13 corneas as the ring region was not found at preparation time in two specimens (animals 2 and 3).

The comparison between groups G1 and G2 showed greater reduction in the group implanted with uncoated rings (FICRS) but the difference was not significant (p=0.061).

In the region adjacent to the ring the number of epithelial cell layers was similar to controls in both groups. Analysis also showed no difference in comparison between groups G1 and G2 (Table 2).

In a region localized between the two regions analyzed in this study (over the rings and at 7mm optical zone), epithelial hypertrophy was observed (Figure 2).

Comparison between regions showed a significant reduction in the number of epithelial cell layers in the area over

the ring in relation to the region adjacent to the ring in both G1 without coating and G2 with coating (Table 3).

TABLE 3 - Comparison of number of epithelial cell layers from G1 and G2 corneas (implanted with intracorneal rings) between the regions (over and adjacent to the ring).

	G1 (n=13)	G2 (n=15)
Over	3 (3;3)	4 (3;5)
Adjacent	6 (5;6)	5 (4;7)
P	0.001	0.003

G1: Group 1 - intracorneal ring implant without coating (FICRS)
G2: Group 2 - intracorneal ring implant with chondroitin sulfate coating (FICRS -CS)
Wilcoxon to compare regions in each group

Spongiosis and hydropic degeneration were seen in both corneal regions studied in G1 and G2 (Figure 3).

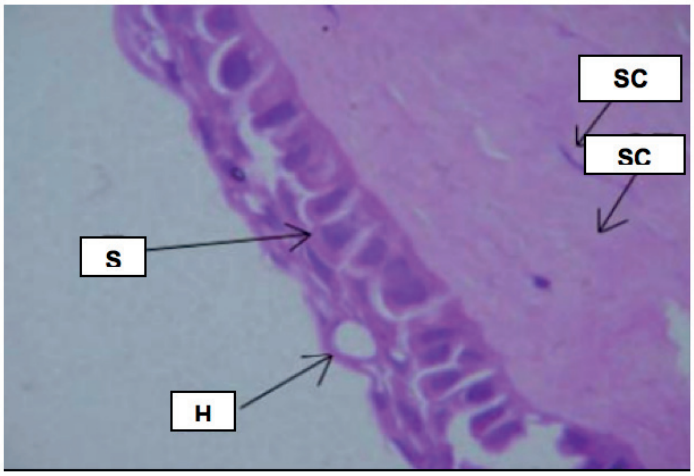

FIGURE 3 - Rabbit cornea of G1. Spongiosis (**S**) and hydropic degeneration (**HD**) (ballooning) intense. Intense stromal compaction (**SC**), HE x1000.

No statistical difference was seen in the percentage of spongiosis or hydropic degeneration between the groups and between the regions in the same group. Nevertheless, the region over the ring showed higher percentages of these alterations (Table 4).

TABLE 4 - Number (n) and Percentage (%) of corneas presenting spongiosis, hydropic degeneration, and basement membrane thinning in right eyes (G1 & G2) in the regions over and adjacent to the ring.

Variable	Region	Group G1 (n=13)	Group G2 (n=15)	p
Spongiosis (%)	Over	69.2	73.3	*1.000*[2]
	Adjacent	30.8	33.3	*1.000*[2]
	P	*0.063*[3]	*0.070*[3]	
Hydropic degeneration (%)	Over	53.8	73.3	*0.433*[2]
	Adjacent	46.2	53.3	*0.705*[1]
	P	*1.000*[3]	*0.453*[3]	
Basement membrane thinning (%)	Over	69.2	46.7	*0.276*[2]
	Adjacent	0.0	0.0	
	P	---	---	

(1) Chi-squared
(2) Fisher
(3) McNemar
(4) G1: Group 1 - intracorneal ring implant without coating (FICRS)
(5) G2: Group 2 - intracorneal ring implant with chondroitin sulfate coating (FICRS-CS)
Mann-Whitney to compare groups in each region
Wilcoxon to compare regions in each group

The basement membrane (MB) displayed thinning in both experimental groups but only in the region over the ring (Figure 4) where its frequency was 22.5% higher in FICRS (Table 4).

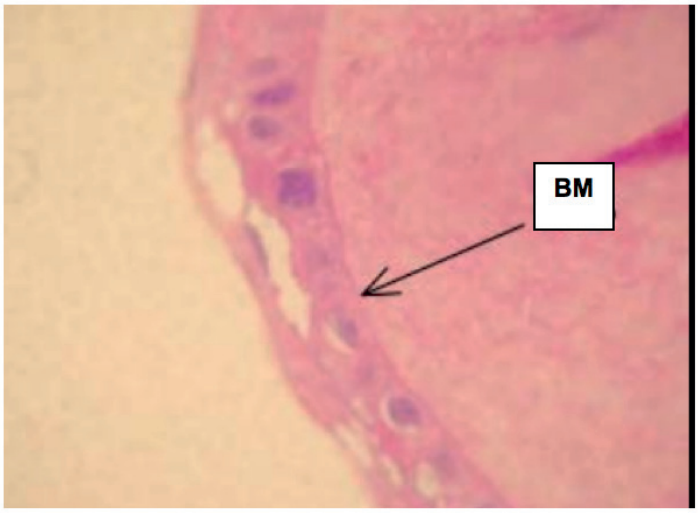

FIGURE 4 - Rabbit cornea from G1. Basement membrane (BM) thinning, PAS (Periodic acid Schiff) x1000.

Intense stromal compaction was observed in the region over the ring in both groups (Figure 2).

Inflammatory cells (lymphocytes, polymorphonuclear

eosinophils and neutrophils and xanthomatous histiocytes) were seen in the stroma adjacent to the ring in G1 (Figure 5). In this region neovascularization was observed 25.2% less in G2 and inflammatory cells 41.7% less in G2 than in G1. Giant cells, histiocytes and pseudocapsule were more frequently observed in G2 by respective margins of 20%, 10% and 26.6% (Table 5 and Figure 6).

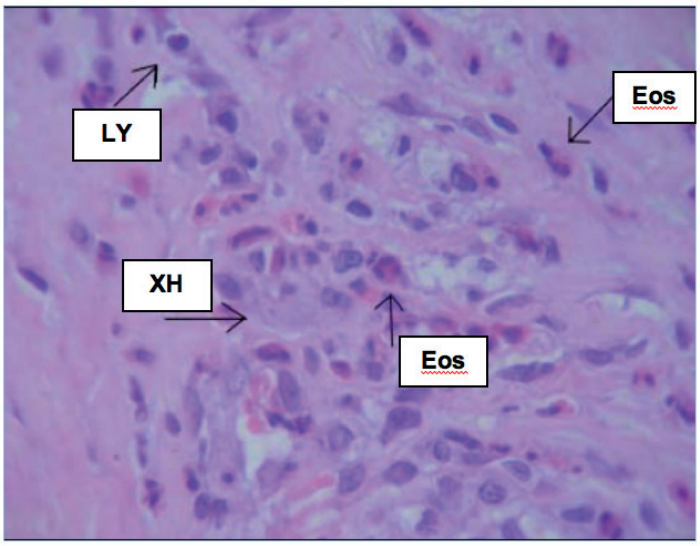

FIGURE 5 - Rabbit cornea from G1 showing lymphocytes (LY), polymorphonuclear eosinophils (Eos), and xanthomatous histiocytes (XH), HE x1000.

TABLE 5 - Percentages (%) of eyes with neovascularization, inflammatory cells, giant cells, histiocytes and pseudocapsule in the stroma from G1 and G2/ by group.

Variable	Group		*p(*)*
	G1 (FICRS)	*G2 (FICRS-CS)*	
Neovascularization	38.5	13.3	0.198
Inflammatory cells	75	33.3	0.054
Giant cells	0	20	0.231
Histiocytes	83.3	93.3	0.569
Pseudocapsule	66.7	93.3	0.139
Descemet's membrane alteration	0	0	---
Endothelium alteration	0	0	---

(*)Fisher's Exact Test or Chi-squared test
G1: Group 1 - intracorneal ring implant without coating (FICRS)
G2: Group 2 - intracorneal ring implant with chondroitin sulfate coating (FICRS -CS)

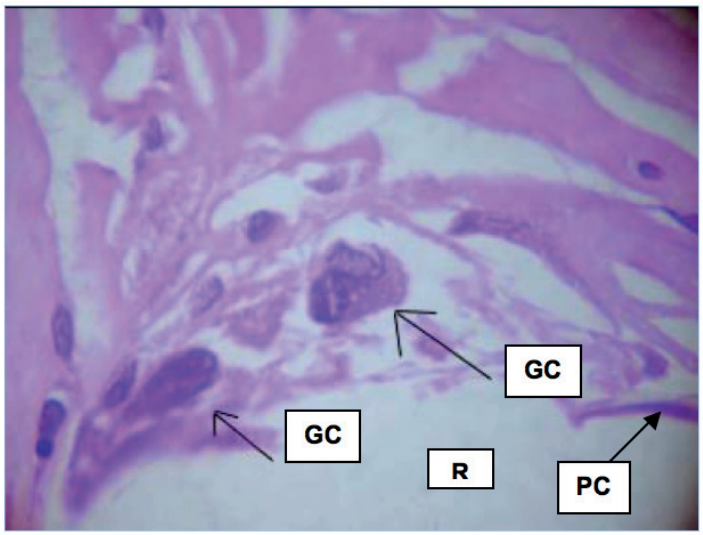

FIGURE 6 - Rabbit cornea of G2 showing giant cells (GC) on the pseudocapsule border (PC) which surrounds the intrastromal ring (R), HE x1000.

Descemet's membrane and the endothelium did not present any alterations in either group.

Discussion

Experimental studies using intracorneal ring implants have been widely performed on the rabbit cornea[22-25], due to its similarity to the human cornea even though it lacks the Bowman membrane.

Histopathological studies of humans cornea implanted with an intracorneal ring are extremely rare due to the difficulty of obtaining these corneas and are only possible in cases with indication of corneal transplant or enucleation. Studies in animal species whose corneas are similar to that of humans enable research studies that would be difficult to perform on humans. Therefore, the present study, which analyzes and compares both histopathological and clinical alterations utilizing two Ferrara intracorneal ring types, would be impossible to perform on human beings.

To the best of our knowledge this is the first study of PMMA intracorneal ring coated with chondroitin sulfate which is one of the mucopolysaccharides naturally occurring in the cornea[21]. Chondroitin sulfate is a glycosaminoglycan present in the matrix of vertebrate connective tissue and is found in the mammalian cornea. In ophthalmology has been used as a wound-healing agent and ocular lubricant. In corneal ulcer and keratoconjunctivitis sicca, chondroitin sulfate exerts anti-inflammatory action. This property of polysulfated glycosaminoglycans is due to its ability to scavenge free radicals, decrease prostaglandin synthesis, block the action

of the complement system and reduce interleukin production[26,27]. These properties may therefore improve ring biocompatibility and reduce complications. Thus, the present study evaluated and compared clinical complications and histopathological alterations in rabbit corneas implanted with two types of Ferrara intracorneal ring segment: the commercially available (without chondroitin sulfate coating) and the Ferrara intracorneal ring segment coated with chondroitin sulfate.

In the present study, clinical evaluation showed that edema decreased in both groups from M1 to M2 and furthermore at M3 (60 days after intracorneal ring implant). The percentage of corneas that showed clinical edema was three times higher in corneas implanted with uncoated rings (FICRS) than those with coated rings (FICRS-CS) (20% versus 6.7%). Corneal edema has been described in many clinical studies in observations that vary from four days to 14 months after surgery[28]. In a study by Hofling-Lima[28], edema occurred in 19.45% of patients who had been implanted with Intacs and Ferrara rings between one week and 22 months post-implant and was associated with infection. The frequency of edema seen in a study by Hofling-Lima[28] was to similar our FICRS-implanted group, but in the present study was not associated with infection probably because it was performed on animals with healthy corneas, by a standardized experimental technique and using prophylactic antibiotic treatment with third generation quinolone.

Similarly to edema, clinical corneal vascularization was more frequent with FICRS (26.7%) than with FICRS-CS (6.7%) and occurred only 60 days after the implant in both groups. Case reports studies described corneal vascularization between 12 months and three years after the intracorneal implant[17, ,28,29]. Nose *et al*.[17] reported vascularization in 50% of cases, a frequency much greater than ours. This discrepancy may be explained by the difference in observation period (60 days in our study), given the possibility that more corneas will develop vascularization with time. But the shorter observation period does not explain the lower percentage of vascularization utilizing rings coated with chondroitin sulfate.

Ring extrusion occurred only in the FICRS-implanted group and was observed 30 days after implant. The extrusion of commercial uncoated intracorneal rings has been described in clinical studies [30,31] where it was reported at 12 months and five years after surgery whereas the extrusion frequency was 13.8% in the Miranda study[31]. In our FICRS-CS group, the absence of extrusion could be related to the lesser inflammation observed that may be due to the lower antigenicity of rings coated with chondroitin sulfate.

Histopathological analysis showed reduction of corneal epithelium layers in the region over the ring in corneas with FICRS compared to controls. There was also a tendency towards reduction under FICRS-CS. Comparing the number of layers over the ring between the groups, FICRS-CS clearly tended to produce less diminution, suggesting that it may provoke fewer clinical complications such as extrusion. The number of corneal epithelial layers was undiminished in the region adjacent to the ring; the reduction is restricted to the zone over the ring and does not compromise the rest of the cornea. The findings of reduced epithelial layers overlying the intracorneal ring are in agreement with the other four histopathological studies found in the literature[25, 32-34], although they did not count the number of layers (quantitative analysis). Samini *et al*.[32], studied eight keratoconic corneas and observed epithelial hypoplasia in five out of eight eyes evaluated after Intacs rings had been removed five to 27 months before keratoplasty. Twa[33] and Spirn[34] described fewer epithelial layers and hipoplasy over the ring implanted in one Ferrara ring case and one Intacs ring, respectively. The only other study on rabbit corneas was performed on five New Zealand rabbits implanted with Intacs and also found fewer epithelial layers over the ring[25]. The reduction in epithelial layers seems to be reversible given that several months after the ring explantation, Samini *et al*.[32] observed normal epithelial thickness above the explantation channel scar.

In contrast to the epithelial layer number, similar frequencies of spongiosis and hydropic degeneration, which are signs of edema, were observed in the corneal epithelium regions above and adjacent to the ring in both groups. These alterations, which have not been described in the other histopathological studies, are typical responses of stratified basal epithelium attacked by inflammatory process that may be intra- and especially intercellular. The edema can break the desmosomes, thus forming small vesicles or areas of greater epithelial fragility. The similarity in frequency between groups suggests that such lesions are caused by surgical trauma and not by the rings.

Thinning of the epithelial basement membrane was displayed in both groups but only in the region above the ring, and was less frequent in the FICRS-CS group. No reference to this alteration was found in the four reported studies, but it may be attributable to inflammatory reaction and type II hypersensitivity.

In the corneal stroma, histopathological examination showed three times higher frequency of neovessels in the FICRS group than in FICRS-CS. The fact that a smaller frequency of neovessels was observed at clinical examination demonstrates that the clinical exam underestimated the presence of neovessels. Clinical and histopathological examination showed smaller

frequency of neovessels in the chondroitin sulfate group. The latter could be directly related to this lower frequency of neovascularization. In experimental ulcers in horses, the corneas treated with chondroitin sulfate showed lower vascularization than those treated without this compound[35].

The frequency of inflammatory cells in corneal stroma was higher in the FICRS group, in which polymorphonuclear eosinophils were predominant, indicating type II hypersensitivity reactions that can be the precursors of stromal neovessels and basement membrane thinning. This lower frequency of inflammatory cells and neovascularization and the absence of extrusion in the chondroitin sulfate group suggest that FICRS-CS is less antigenic. But immunohistochemical study of angiogenesis stimulating factors is required to establish the etiology of these neovessels.

The fact that giant cells were present only in the FICRS-CS group is indicative of macrophage migration, whose interaction with the ring can lead to type IV hypersensitivity late inflammatory reaction that when associated with histiocyte proliferation induced up to a 26.6% higher frequency of pseudocapsule formation. A pseudocapsule may represent an adaptation of the cornea to the ring and we suppose that it provides a possible way for reducing antigenic reaction. The PMMA could be an antigenic agent while the addition of corneal matrix component substances to the rings such as chondroitin sulfate could lead to a closer ideal biocompatibility. PPMA is generally described as inert and well tolerated material but lipidic keratopathy has been a common finding in human implanted intracorneal PPMA rings[33] suggesting that it is not totally biocompatible.

Our results showed both clinical and histopathological advantages derived from the chondroitin sulfate coating of the rings in rabbits with healthy corneas. These findings lead us to suppose that such coating may also be beneficial to diseased human corneas. The mechanism by which the chondroitin sulfate leads to these benefits may be through its antiinflammatory action, or via the "encapsulation".

The scarceness of this type of study and the different responses resultant from the two ring types should serve as a stimulus for new experimental studies with longer follow-up and immunohistochemical evaluation in order to obtain better intracorneal implants, especially given their widespread use in very young patients with a long life expectancy.

Conclusion

Ferrara intracorneal rings coated with chondroitin sulfate (FICRS-CS) caused lower frequency of clinical and histopathological alterations than Ferrara intracorneal rings without the coating (FICRS), demonstrating higher biocompatibility of the FICRS-CS.

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