(Un)Safety of a Hydrogel Corneal Inlay to Correct Presbyopia: 5-Year follow up

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RESUMO

Introdução: Aprovado em Junho de 2016 pela U. S. Food and Drug Administration (FDA), o implante corneano de hidrogel Raindrop®, desenhado para a correção da presbiopia, modifica a zona central da superfície anterior da córnea, criando uma região hiper-prolata com maior poder de focagem para perto e para a distância intermédia. Até à data não existem estudos na literatura com follow-up superior a 1 ano após a inserção deste implante.

Objetivo: Avaliar a segurança e eficácia a longo prazo do implante corneano de hidrogel Raindrop® no tratamento da presbiopia.

Métodos e Material: Estudo retrospetivo de série de casos de olhos presbíopes submetidos a inserção de implante corneano de hidrogel (Raindrop®) no olho não dominante. Foi recolhida informação clínica, nomeadamente acuidade visual, período de seguimento, intervenções cirúrgicas, biomicroscopia e topografia corneana.

Resultados: Foram incluídos 6 doentes previamente submetidos a implante intracorneano de hidrogel (Raindrop®). Três implantes foram explantados devido a baixa acuidade visual por *haze* corneano relacionado com o implante. Num dos casos ocorreu *melting* da córnea sobre o implante, com exposição do mesmo, apesar do longo tempo decorrido desde a sua implantação (5 anos). O aparecimento de *haze* corneano ocorreu nos 6 doentes, que variou entre moderado a grave. O período mínimo de follow-up foi de 2 anos e o máximo de 5 anos.

Conclusão: Este é o primeiro estudo em doentes com implante intracorneano de hidrogel Raindrop® com follow-up mínimo de 2 anos. Os nossos resultados mostram que este implante, aprovado em 2016 pela FDA, apresenta um mau perfil de segurança a longo prazo, devido à presença de *haze* e *melting* da córnea, com consequente necessidade de explantação num elevado número de casos.

Palavras chave: Implante corneano de hidrogel; Raindrop®; presbiopia.

ABSTRACT

Introduction: Approved in June 2016 by the *U.S. Food and Drug Administration* (FDA), the hydrogel corneal implant Raindrop®, designed for the correction of presbyopia, modifies the central zone of the anterior surface of the cornea, creating a hyper-prolate region with higher power focus for near and for intermediate distance. Up to date there are no studies in the literature with follow-up over 1 year after insertion of the implant.

Objective: To evaluate the long-term safety and efficacy of hydrogel corneal implant Raindrop® for the treatment of presbyopia.

Methods and Material: Retrospective study of cases of presbyopic eyes undergoing insertion of a hydrogel corneal implant (Raindrop®) in the non-dominant eye. Clinical information was collected, including visual acuity, follow-up time, surgery interventions, biomicroscopy and corneal topography.

Results: Six eyes of 6 patients previously submitted to hydrogel intracorneal implant (Raindrop®) were included. Three implants were explanted due to low visual acuity, secondary to the presence of corneal haze, associated with the implant. In one case there was melting of the cornea above the implant, followed by its exposure, despite the long time since its implantation (5 years). The presence of corneal haze occurred in 6 patients, ranging from moderate to severe. The minimum follow-up period was 2 years and the maximum was 5 years.

Conclusions: This is the first study in patients with the hydrogel corneal implant Raindrop® with minimum follow-up of 2 years. Our results show that this implant, approved by FDA in 2016, has a poor long-term safety profile due to the presence of corneal haze and melting, with the consequent need to explant a large number of devices.

Keywords: Hydrogel corneal implant; Raindrop®; presbyopia.

INTRODUCTION

Presbyopia is an age-related reduction in the amplitude of crystalline lens accommodation, causing loss of uncorrected near visual acuity (UNVA).[1,2] There are several surgical approaches to treat presbyopia, based either on a corneal, lenticular or scleral intervention, attempting to restore the defocusing ability of the eye.[1] Briefly, techniques with corneal approach include excimer laser procedures in which the dominant eye is corrected for distance vision and the other eye for near vision; multifocal corneal ablation, where the peripheral cornea is ablated, creating a negative peripheral asphericity; conductive keratoplasty, consisting of application of low frequency radio waves to contract collagen fibrils within the mid-peripheral cornea; intrastromal devices that induce a biomechanical change in the corneal tissue leading to a central steepening of 1–2 diopters; and corneal inlays with a pinhole aperture increasing the depth of focus.[1,2,3] Corneal inlays have the advantage of not removing tissue, can be combined with laser refractive and cataract surgery, and in case of complications are removable.[4]

There are 4 corneal inlay designs for use in presbyopic eyes.[5] The Raindrop Near Vision Inlay® (ReVision Optics, LakeForest, California, USA) modifies the central zone of the anterior surface of the cornea by inducing a central hyper-prolate region with higher power focus for near and

for intermediate distance.[1,2] It is thicker at the center and thinner at the edges, limiting the near-power effect to the center of the pupil.[6] Formerly known as Vue+® or Presbylens®,[7] it was approved in June 2016 by the *U.S. Food and Drug Administration* (FDA) for the correction of presbyopia. It consists in a hydrogel inlay with 2.0 mm diameter and a central thickness of 32 to 36 µm,[6] to be implanted in the nondominant eye in a corneal stroma pocket or under a 130 to 150 µm laser-assisted in situ keratomileusis (LASIK) flap, created with a femtosecond laser. [3,5,6]

The Kamra® inlay (Acufocus, Inc.) consists in a small aperture, which functions as a pinhole, to increase the depth of focus, without changing the refractive status of the cornea. The FlexivueMicrolens® (PresbiaCooperatief U.A.) and InVue® (Biovision AG, Neoptics AG) are similar, both having a near addition power in a peripheral zone and no power in the central zone, thus providing a bifocal effect.[2,8]

Up to date there are no studies in the literature with follow-up longer than 1 year after insertion of the Raindrop® implant. The purpose of this study is to evaluate the long-term safety and effectiveness of this hydrogel corneal implant for the improvement of UNVA in emmetropic presbyopic patients.

METHODS AND MATERIAL

Retrospective study performed at the Ophthalmology Department of Centro Hospitalar e Universitário de Coimbra involving patients previously submitted to insertion of a hydrogel corneal implant (Raindrop®) in the non-dominant eye. Informed consent was obtained from all patients and the study followed the assumptions of the Helsinki Declaration. Collected clinical information included visual acuity, follow-up time, surgery interventions, biomicroscopy and corneal topography.

The inclusion criteria when the implants were inserted were: presbyopic subjects older than 45 years old; a preoperative spherical equivalent (SE) of -1.0 to +1.0 diopter (D); a refractive cylinder of +1.0D or less; a preoperative UNVA of 0.40 logMAR or worse in the nondominant eye; an uncorrected distance visual acuity (UDVA) of 0.20 logMAR or better in each eye; no amblyopia; central corneal thickness ≥ 500 µm; endothelial cell density ≥ 2000 cells/mm^2; and finally, a stable refraction for at least 12 months before corneal inlay implantation. Patients with previous ocular surgery, decentered pupil, severe dry eye, severe corneal aberrations or with any other anterior segment ocular disease or systemic disorder that could interfere with the normal healing process, were excluded.

Clinical examinations consisted in near, intermediate and distance visual acuity (VA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts; biomicroscopy and fundoscopy examination; keratometry; Goldmann applanation tonometry and corneal topography (Orbscan II, Bausch & Lomb, Rochester, New York) and tomography (Pentacam, Oculus Optikgerate GmbH, Wetzlar, Germany) Endothelial cell density was assessed with the specular microscope (Tomey EM-3000, Nagoya, Japan).

RESULTS

This study included 6 eyes, of 6 patients, (3 female and 3 male), with a mean age of 52.7 ± 3.2 years (range 48 to 58 years). The mean follow-up period was of 65.9 ± 4.6 months (range 63.8 to 76.6).

All patients presented corneal haze, ranging from moderate to severe according to Hanna's scale. Three raindrop inlays (50%) had to be explanted due to the presence of corneal haze, which impaired VA. The explantation occurred at the 5th, 39th and 60th months postop. One of these cases showed corneal melting above the inlay (**Figures 1 and 2**), followed by its exposure, 5 years after implantation (video supplemental material).

At the 1st month after corneal inlay implantation, the operated eye showed UCNVA of 0.22 ± 0.10, BCNVA of 0.07 ± 0.04, UCIVA of 0.42 ± 0.12 and BCDVA of -0.01 ± 0.05 (logMAR). At the 1st year of follow-up, UCNVA was 0.17 ± 0.13, UCIVA was 0.03 ± 0.05, and BCDVA was 0.07 ± 0.08. At 2 years of follow-up, UCNVA decreased to 0.37 ± 0.09 and BCDVA to 0.11 ± 0.09 (n=6).

At the end of follow-up, 3 patients still had the corneal inlay, presenting UCDVA ranging from 0.7 to 0.2 logMAR, and needed an addition of +1,75 to+2,00 D for near correction.

CASE 1

A 53-year-old man presented UDVA of 0.0 logMAR, UIVA of 0.5 logMAR and UNVA of 0.5 logMAR, BCNVA was 0.0 logMAR with +3.00D in the left eye. He was submitted to a Raindrop® implant in the left eye, without complications. In the 1st postoperative month, the patient maintained UDVA, UIVA and BCNVA and showed an improvement of UNVA. The biomicroscopy showed a well centered implant and fundoscopy was normal. Two years after surgery, he presented a decrease of BCDVA (0.3 logMAR) and BCNVA (0.3 logMAR) and corneal haze above the inlay was observed. Because of the impaired vision, both for distance and for near, explantation of the corneal inlay was performed.

One year after the explant, BCDVA in left eye was 0.1 logMAR and BCNVA 0.0 logMAR with +2.25 D.

CASE 2

A 50-year-old man, emmetrope with BCNVA of 0.0 logMAR with +2,00 D in the nondominant eye (left eye), attended to our department in order to stop wearing spectacles for near vision. The patient was submitted to the implantation of a Raindrop® inlay in the left eye, and the surgery occurred without complications. One month after surgery, the UNVA was 0.2 logMAR and 0.0 logMAR with +2.00 D. The remaining clinical exam did not reveal alterations. One year after the intervention, both the UDVA and UNVA were 0.0 logMAR, and showed corneal haze grade 1. During de 2nd, 3rd and 4th years there was worsening of the corneal haze, with consequent impaired vision. Five years after the implant, the patient had UDVA and BCNVA of 0.3 logMAR, and presented corneal haze grade 4 and melting above the inlay (**Figures 1 and 2**).

Figures 1 and 2 - Corneal haze and melting five years after implantation of the corneal inlay.

The corneal inlay was removed (video supplemental material). One week after the explant, the patient had UDVA of 0.7 logMAR and UNVA of 0.8 logMAR. Slit lamp examination showed corneal haze. Two months later, the UDVA was 0.8logMAR, the BCDVA with 2.25 diopters was 0.1 logMAR and the BCNVA was 0.0 logMAR. Corneal topography showed a low with-the-rule astigmatism and central flattening in the area where the implant was located and where melting had occurred **(Figure 3)**. Corneal haze remained in the previous inlay's location, but no epithelial ingrowth had occurred (**Figure 4)**

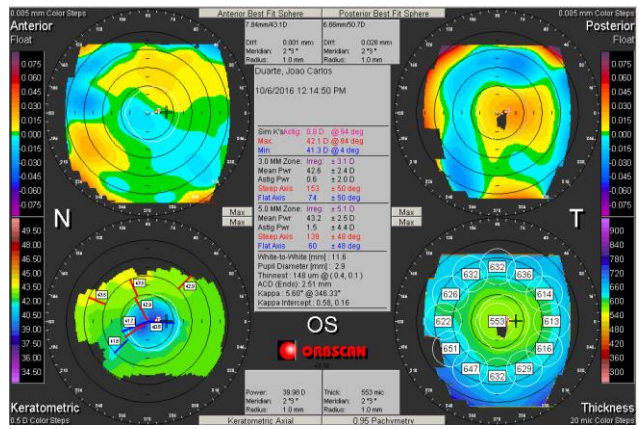

Figure 3 - Corneal topography two months after the explantation. A low with-the-rule astigmatism and a central flattening in the previous inlay's location are visible.

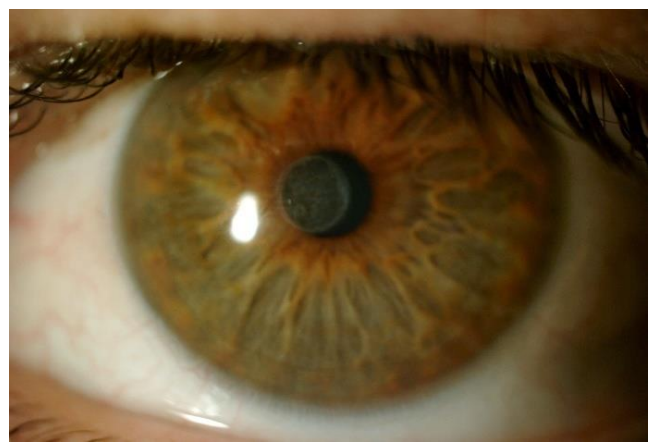

Figure 4 - Corneal haze in the inlay's former location.

CASE 3

A 52-year-old man, emmetrope with BCNVA of 0.0 logMAR with +2,50 D in the nondominant eye (left eye), attended to our department wishing for spectacle independence. A Raindrop® inlay implantation was performed in the left eye, and the surgery occurred without complications. One month after the surgery, the patient showed a decrease of the UDVA (0.2 logMAR). The UIVA was 0.4 logMAR, the UNVA was 0.2 logMAR and the BCNVA was 0.1 logMAR with +2.00 D. One year later, both UDVA and UNVA were 0.2 logMAR, with corneal haze grade 2. Until the last follow-up visit, at 60 months, the patient maintained the UDVA (0.2 logMAR) and the BCNVA (0.2 logMAR) with +2.00D, without worsening of the corneal haze.

CASE 4

A 58-year-old woman attended our department in order to stop wearing spectacles for the near vision. The UDVA was 0.0 logMAR and BCNVA 0.0 logMAR with +2.00 D in the nondominant eye (right eye). Eight months after surgery, the corneal inlay was removed due to the corneal haze grade 3 that substantially impaired her vision (**Figure 5**). Two years after the explant, BCDVA was of 0.3 logMAR, which was attributed to retinal disease (pattern dystrophy).

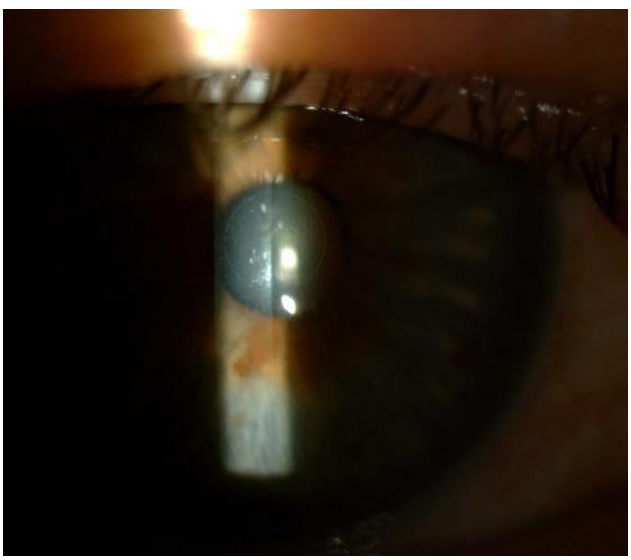

Figure 5 - Corneal haze grade 3, eight months after implantation of the corneal inlay.

CASE 5

A 48-year-old woman, emmetrope with BCNVA of 0.0 logMAR with +1.75 D in the nondominant eye (left eye), attended to our department in order to stop wearing spectacles for near vision. We performed a Raindrop® inlay implantation, without complications during surgery. One month later, the patient presented a reduction in the UDVA (0.7 logMAR) and UNVA (0.4 logMAR) and corneal haze was observed at slit-lamp examination. From one year after surgery up to the 4th year follow-up visit, the subject had an UDVA of 0.7 logMAR and a BCDVA of 0.0 logMAR. The UNVA was 0.3 logMAR and the BCNVA was 0.2 logMAR. At this time the patient presented no corneal haze.

CASE 6

A 56-year-old woman, with UDVA of 0.5 logMAR, BCDVA of 0.0 logMAR and BCNVA of 0.0 logMAR with +2.50 D in the nondominant eye (left eye) was implanted with the Raindrop® inlay in the left eye without complications. One month later, the patient presented a slight decrease of the BCDVA (0.1 logMAR) and UNVA (0.1 logMAR), with corneal haze grade 1. One year after the surgery, she maintained both distance and near visual acuity. At the third year of follow up, she showed a decreased UNVA (0.5 logMAR). BCNVA and BCDVA were of 0.1 logMAR. A central annular area with corneal haze grade 1 was observed on slit-lamp examination.

Case 1	Inlay explanted at 39th month of follow up		
Case 2	Inlay explanted at 60th month of follow up		
Case 3	**VA**	**1st month visit**	**Last follow up visit**
	UDVA	0.2 logMAR	0.2 logMAR
	UNVA	0.2 logMAR	0.2 logMAR
	BCNVA	0.1 logMAR	0.2 logMAR
Case 4	Inlay explanted at 8th month of follow up		
Case 5	**VA**	**1st month visit**	**Last follow up visit**
	UDVA	0.7 logMAR	0.7 logMAR
	UNVA	0.4 logMAR	0.3 logMAR
	BCNVA	0.1 logMAR	0.2 logMAR
Case 6	UDVA	0.1 logMAR	0.2 logMAR
	UNVA	0.1 logMAR	0.5 logMAR
	BCNVA	0.0 logMAR	0.1 logMAR

Table 1 - Brief summary of the 6 cases reported. Visual acuities correspond to 1st month and last follow up visits.

DISCUSSION

Recently, various surgical approaches have been used to treat presbyopia. Corneal inlays are monocular devices implanted in the corneal stroma, through an intrastromal tunnel created using a femtosecond laser, in order to improve near visual acuity while maintaining distance vision.[9]

This is the first study in patients with the hydrogel corneal implant Raindrop® with a follow-up longer than one year.

During the study, five patients had recurrent corneal haze that required explantation of the inlay in three cases. The mean BCDVA was 0.7 logMAR, 0.1 logMAR and 0.3 logMAR within 1 week, 1 month, and 2 years after explantation, respectively. The remaining three patients still have the inlay, with UNVA ranging from 0.3 to 0.5 logMAR at the last follow up visit. Corneal haze appeared from the 1st week to the 7th month, impairing vision.

Several studies report high satisfaction levels regarding the implantation of intracorneal inlays for correction of presbyopia, with subjective complaints similar to those after LASIK.[4,7] The most common complications are epithelial ingrowth, corneal stromal opacity, glare, halos, dry eye, and night vision problems. UDVA is reported to not being significantly affected by the corneal inlay, with the majority of patients remaining satisfied for distance vision.[10,11,12]

Iv et al,[13] demonstrated a high efficacy for the KAMRA corneal inlay in a sample of 507 eyes, improving near vision in emmetropic presbyopes and with minimal impact on UDVA and mesopic contrast sensitivity, 18 months after the implant. In a 60 month follow-up study, Alois et al[14] observed a statistically significant decrease in UNVA, UIVA and UDVA between 36 and 60 months after the the KAMRA corneal inlay implantation, which the authors attributed to normal age-related hyperopic refractive shift. Corneal epithelial iron deposits were noted in 56.3% of the eyes at 36 months of follow-up. These iron depositions were attributed to alterations in tear film thickness, namely its composition, and corneal epithelial basal cell storage.[15] We have not seen this complication with the Raindrop® inlay. Although Ylmaz et al[16] concluded that intracorneal inlay implantation was a safe procedure, he described four cases of inlay explantation in a 4-year study involving 39 eyes: two due to flap complications (a buttonhole and a thin flap) and two due to refractive shifts (myopic and hyperopic). Five cases of infectious keratitis following corneal inlay implantation were reported by Duignan et al[9]. All patients lost vision and two corneal inlays were explanted.

Favorable outcomes were reported for the Flexivue® Micro-Lens intracorneal inlay in a 12-month study, in which the only reported complication was the presence of halos and glare in 12,5% of patients.[17] Malandrini et al[2] studied a population of 26 eyes submitted to corneal inlay implantation using a 150 kHz femtosecond laser (iFS). He described an improvement of UNVA 36 months after surgery (0.10 logMAR) compared to the mean preoperative UNVA (0.76 logMAR). UDVA decreased from 0.00 logMAR to 0.15 logMAR at preop and 36 months, respectively. Regardless of these good results, the authors also noticed an increase of mean spherical aberration after surgery, and the device explantation had to be performed in 6 eyes because of halos, glare and reduced UDVA.

Chayet et al,[6] showed good results in 16 hyperopic patients submitted to LASIK and Raindrop® corneal inlay in the nondominant eye, with UNVA of $\geq$20/27 (0.1 logMAR) at all visits. However, one inlay was explanted after only one year of follow-up. Garza et al[18], compared these results with those obtained in 20 emmetropic and 30 myopic patients. At 1 year, 7% of myopic patients were dissatisfied with the intervention. The efficacy profile was similar in the 3 populations. Arguably, the authors concluded that the procedure was safe and effective over a 1-year follow-up. Indeed, our results point to a further decrease in safety and efficacy with a longer follow-up.

Up to date there are no studies in the literature with more than 1 year of follow-up after insertion of the Raindrop® inlay. Mulet et al[19] conducted a 5-year study of 34 hyperopic eyes implanted with another hydrogel corneal inlay (Permavision®, Anamed, Lake Forest, CA) and reported progressive perilenticular deposits and corneal haze in the majority of cases, with consequent deterioration of visual acuity. The corneal inlay was explanted in 58,8% of cases. Our results are in accordance with this study and one of our patients also developed a perilenticular opacity. As assessed by studies with pathologic and confocal microscopy analysis, this manifestation seems to result from the migration of epithelial cells and their ingrowth on the inlay surface.[20]

One of the advantages attributed to corneal inlays is its reversible character.[5,21] However, we observed a case of corneal melting that ended in the explantation of the inlay and permanent corneal lesion. Even milder cases had persistent corneal haze after the inlay removal.

Our results show that this implant, approved by FDA this year, has a poor long-term safety profile due to the presence of corneal haze and melting, with the consequent need to explant a significant proportion of cases.

The present study has numerous limitations, such as its retrospective nature and a small sample size. There is an ongoing shift towards the recognition of the importance of reporting or publishing bad/negative outcomes. As such, from our experience, we feel obliged to not recommend the Raindrop® inlay implantation for presbyopia correction, due to the possibility of serious complications occurring several years after surgery.

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