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Intrastromal corneal ring segment implantation in pediatric patients with keratoconus: long-term follow-up

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Purpose: *To evaluate the long-term outcomes of Intrastromal Corneal Ring Segments (ICRS) implantation in pediatric patients with keratoconus.*

Methods: *Retrospective analysis of eyes with ICRS implantation in pediatric age. Uncorrected (UCVA) and best-corrected (BCVA) visual acuity, maximum and minimum keratometry (Kmax and Kmin), and corneal thickness at the thinnest point (CTTP) were evaluated preoperatively, 6 to 12 months after surgery, 5 years after surgery, and at the last follow-up visit (>10 years after surgery).*

Results: *Fourteen eyes (10 patients) were included. In 5 eyes all ICRS were explanted and in 1 eye, one of the segments was explanted. UCVA ($p=0.028$) and BCVA ($p=0.028$) improved 6 to 12 months after surgery and remained stable afterwards ($p>0.999$). There was a decrease in Kmax and Kmin 6 to 12 months after surgery ($p<0.001$ and $p=0.012$, respectively), with subsequent stability at the 5-year follow-up ($p=0.736$ and $p=0.056$, respectively). Kmax remained stable at the last follow-up ($p>0.999$) but there was an increase in Kmin ($p=0.028$). There were no changes in CTTP ($p=0.097$).*

Conclusion: *ICRS implantation seems to be a minimally invasive, and reversible procedure that leads to improvement of BCVA and keratometry readings. Despite this, the need for explantation increased overtime.*

Introduction. Keratoconus is a progressive and asymmetrical disorder caused by changes in corneal collagen organization. This results in the development of a progressively more conic-shaped cornea, that leads to irregular astigmatism, progressive myopia, corneal thinning, optic aberrations and poor visual acuity. [1]. In more advanced stages of the disease, Vogt striae, a Fleischer ring, scarring, and hydrops may develop. [2]

Usually, keratoconus manifests in the second decade of life and it may progress until the third to fourth decade. [2]. Pediatric keratoconus tends to be more aggressive, due to the higher rate of corneal collagen remodeling, with increased risk of developing corneal opacities and need of subsequent keratoplasty. [1, 3]. Furthermore, pediatric keratoconus is usually more advanced at the time of diagnosis. [1].

Treatment options available include use of spectacles, contact lenses, intrastromal corneal ring segments (ICRS), corneal collagen cross-linking, and anterior lamellar or penetrating keratoplasty. [4] Conservative management usually begins with spectacle or contact lenses correction, but, in children, they are frequently not well tolerated or insufficient to provide a satisfactory visual acuity. [3] In patients with documented or perceived risk of progression, cross-linking is considered the mainstay of treatment, increasing biomechanical corneal strength and stability due to collagen photopolymerization mediated by reactive oxygen. [3] Some studies report an improvement in spectacle BCVA after cross-linking, but, despite this, a metanalysis conducted by Kobashi et al showed that this improvement does not seem clinically significant, since the gain is inferior to a line in the eye chart, which is within the expected by the test-retest variability. [5] On turn, ICRS improve myopia and astigmatism with an arc-shortening effect that flattens the central cornea and reduces visual distortion, and may be used in mild to moderate cases with contact lenses intolerance and/or insufficient visual improvement with spectacles or contact lenses. [4] Lastly, corneal transplantation is usually reserved for advanced cases, due to the risk of graft rejection and other complications. [6]

Many studies demonstrated the efficacy of ICRS implantation in increasing visual acuity and reducing refractive and keratometric values in patients with keratoconus. [7–10] Despite this, very few studies evaluate the outcomes of ICRS implantation in children. Furthermore, it is known that visual impairment in pediatric patients can affect their social and educational development, having a negative impact in the child's quality of life. [1] Taking this into consideration, our purpose is to evaluate the long-term outcomes of ICRS implantation in pediatric patients with keratoconus.

Materials and methods

Retrospective study that included consecutive patients aged ≤18 years old submitted to ICRS implantation to treat progressive keratoconus at the Ophthalmology Department of Centro Hospitalar Universitário de Santo António, between January 2008 and July 2011. Only patients with at least 10 years of follow-up were included. All patients had been diagnosed with keratoconus with reported progression in the 6 months before surgery and had unsatisfactory visual acuity with spectacle or contact lenses correction or contact lenses intolerance. Exclusion criteria for ICRS implantation were uncontrolled atopy, keratometry >60 D and significant apical opacities or scarring, previous history of acute hydrops or corneal thickness <400 μm in the planned site of ICRS implantation. The implanted ICRS were Intacs® or Intacs SK® (Addition Technology, Inc. Lombard, Illinois, USA). Surgeries were performed by three experienced corneal surgeons (P.T., L.O., M.G.) that used a standard approach, consisting of tunnel creation by mechanical dissection, followed by ICRS implantation according to a preoperative plan and an implantation nomogram provided by the manufacturer. Postoperative medication consisted of a combination of a topical antibiotic and steroid for 10 days.

Demographic, clinical, and topographic data were recorded. Uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) were assessed using the logMAR scale. Maximum keratometry (Kmax), minimum keratometry (Kmin), and corneal thickness at the thinnest point (CTTP) were evaluated using the Orbscan II® corneal topography system (Bausch & Lomb, Orbtek Inc., Salt Lake City, UT). UCVA, BCVA, keratometry values and CCTP were evaluated before surgery, 6 to 12 months after surgery, 5 years after surgery and at the last follow-up visit (minimum 10 years). The need for ICRS explantation and additional procedures performed were also recorded. Only eyes that still had at least one ICRS were included at each follow-up evaluation.

This study complied with the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board. All patients gave written informed consent after proper patient confidentiality was ensured. Statistical analysis was performed using IBM® SPSS® Statistics version 26. Categorical variables are summarized as absolute and relative frequencies. Continuous variables are summarized as mean ± standard deviation. Normality of data was evaluated with the Shapiro-Wilks test. Repeated-measures analysis of variance followed by post-hoc Bonferroni correction were performed to evaluate the evolution of parameters overtime. A p-value inferior to 0.05 was considered statistically significant.

Results

Fourteen eyes of 10 individuals were included in this study. Mean age at the time of surgery was 15.5 ± 3.0 years old, 60.0% were male and the mean follow-up time was 11.9 ± 1.1 years. In 11 eyes (78.6%), 2 segments were implanted, and in 3 eyes (21.4%), only 1 segment was implanted. All surgical procedures were uneventful.

In 5 eyes (35.7%), all implanted segments were explanted, and in 1 eye (7.1%), one of the two segments was explanted. In 66.7% of these cases, the ICRS was explanted more than 9 years after surgery. Time and causes of explantation are detailed in Table 1, as well as additional procedures eventually done in each case. Taking this into consideration, at 6 to12 months and 5-years' time-points 13 eyes were evaluated, and at the last follow-up 9 eyes were included for statistical analysis.

Concerning the patients with the ICRS not explanted, and compared to the baseline, there was a significant improvement in the logMAR BCVA (0.4±0.3 vs 0.8±0.4, p=0.028) and in the logMAR UCVA (0.7±0.3 vs 1.3±0.6, p=0.028) at the 6 to 12 months visit (n=13). Both logMAR BCVA and logMAR UCVA remained stable from the 6 to 12 month visit until the last follow-up visit (0.4±0.4 vs 0.3±0.3, p>0.999 and 0.6±0.3 vs 0.7±0.4, p>0.999, respectively, n=9). At the 6 to 12 month visit (n=13), comparing to the baseline, 9 (69.2%) eyes improved at least 2 logMAR lines, and 6 eyes (46.2%) had an improvement equal or superior to 3 logMAR lines in the BCVA. None of the eyes lost visual acuity lines. At the 5-year follow-up visit (n=13), 10 eyes (76.9%) improved at least 1 line in the logMAR scale, and 8 (61.5%) eyes improved at least 6 logMAR lines, compared to the baseline. One eye lost one line of BCVA. At the last follow-up visit (n=9), comparing to the baseline, all the 9 eyes still with ICRS in place had at least 3 logMAR lines of improvement of BCVA and 6 (66.7%) eyes improved at least 6 lines. Visual acuity evolution is summarized in Table 2.

Mean Kmax decreased from 56.4±4.7 D at baseline to 51.6±3.9 D at the 6 to 12 months visit (p<0.001) and Kmin decreased from 48.5±3.7 D at baseline to 44.4±4.2 D at 6 to 12 months (p=0.012, n=13). Subsequent stability was observed in Kmax after 5 years (52.2±4.6 D vs 51.6±3.9 D, p=0.736, n=13) and at the last follow-up visit (50.8±2.0 D vs 50.9±3.0 D, p>0.999, n=9). Kmin remained stable at the 5-year visit (45.8±3.9 D vs 44.4±4.2

Table 1. Patients submitted to ICRS explantation

	Cause	Time after surgery (y)	Additional procedures
1	Extrusion	<1	None
2	Extrusion	1.5	None (1 segment remains)
3	Unsatisfatory VA	9	DALK
4	Extrusion	11	New ICRS
5	Unsatisfactory VA	12	DALK
6	Unsatisfactory VA	12	DALK

Legends: VA – Visual acuity; Y – years; DALK – Deep anterior lamellar keratoplasty ; ICRS – Intrastromal corneal ring segment

Table 2. Visual acuity evolution

Variable	Compared period	n	Compared values (mean± SD, logMAR)	p-value
UCVA	Pre-operative vs month 6-12	13	1.3±0.6 vs 0.7±0.3	0.028*
	Pre-operative vs last follow-up	9	1.6±0.5 vs 0.7±0.4	0.048*
	Month 6-12 vs year 5	13	0.7±0.3 vs 0.6±0.4	>0.999
	Month 6-12 vs last follow-up	9	0.6±0.3 vs 0.7±0.4	>0.999
BCVA	Pre-operative vs month 6-12	13	0.8±0.4 vs 0.4±0.3	0.028*
	Pre-operative vs last follow-up	9	1.0±0.3 vs 0.3±0.3	0.032*
	Month 6-12 vs year 5	13	0.4±0.3 vs 0.3±0.2	>0.999
	Month 6-12 vs last follow-up	9	0.4±0.4 vs 0.3±0.3	>0.999

Legends: UCVA – Uncorrected visual acuity; BCVA – Best-corrected visual acuity; SD – Standard Deviation; * Statistically significant

Table 3. Keratometry and corneal thickness evolution

Variable	Compared period	n	Compared values (mean ± SD)	p-value
Kmax	Pre-operative vs month 6-12	13	56.4±4.7 vs 51.6±3.9 D	<0.001*
	Pre-operative vs last follow-up	9	56.7±4.2 vs 50.8±2.0 D	0.003*
	Month 6-12 vs year 5	13	51.6±3.9 vs 52.2±4.6 D	0.736
	Month 6-12 vs last follow-up	9	50.9±3.0 vs 50.8±2.0 D	>0.999
Kmin	Pre-operative vs month 6-12	13	48.5±3.7 vs 44.4±4.2 D	0.012*
	Pre-operative vs last follow-up	9	48.5±4.0 vs 45.7±2.9 D	0.060
	Month 6-12 vs year 5	13	44.4±4.2 vs 45.8±3.9 D	0.056
	Month 6-12 vs last follow-up	9	43.4±3.1 vs 45.7±2.9 D	0.028*
CTTP	Pre-operative vs month 6-12	13	412.4±42.9 vs 380.0±51.5 µm	0.054
	Pre-operative vs last follow-up	9	402.8±46.9 vs 365.4±34.3 µm	0.097
	Month 6-12 vs year 5	13	380.0±51.5 vs 392.7±47.3 µm	0.810
	Month 6-12 vs last follow-up	9	359.1±43.8 vs 365.4±34.3 µm	>0.999

Legends: Kmax – Keratometry at the steepest axis; Kmin – Keratometry at the flattest axis; CTTP – Corneal thickness in the thinnest point; SD – Standard Deviation; D – Diopters; * Statistically significant

D, p=0.056, n=13) and increased at the last follow-up (45.7±2.9 D vs 43.4±3.1 D, p=0.028, n=9), compared to 6 to 12 months after surgery. There were no statistically significant changes in CTTP 6 to 12 months after ICRS implantation (380.0±51.5 µm vs 412.4±42.9 µm, p=0.054, n=13) nor at 5 years (392.7±47.3 µm vs 380.0±51.5 µm, p>0.525, n=13) or at the end of follow-up (365.4±34.3 µm vs 359.1±43.8 µm, p>0.999, n=9), comparing to months 6 to 12. The evolution of the keratometric readings and CTTP are summarized in Table 3.

Regarding the security profile, two patients with bilateral ICRS were symptomatic. One patient had dysphotopsia complains in both eyes, that developed after ICRS implantation. The other patient complained of glare in one eye, that developed 3 years after ICRS implantation. In both cases, patients could tolerate the symptoms, and did not require ICRS explantation.

Discussion

This study presents the long-term results of ICRS implantation in pediatric patients with progressive keratoconus. Only patients with more than 10 years of follow-up were included, which turns this study, to our best knowledge, into the one with the largest follow-up period in this topic.

Fourteen eyes were included in our study, and 9 reached the last follow-up visit with ICRS in place, meaning that 5 eyes needed to explant all the ICRS implanted. Additionally, in 1 eye, one of the two segments was explanted. In 3 eyes, there was ICRS extrusion (2 in the first two years and 1 after 11 years). Three eyes were submitted to DALK (1 after 9 years and 2 after 12 years of follow-up).

Considering the eyes with ICRS in place at the last follow-up visit, there was a significant initial improvement of UCVA and BCVA, and a decrease of Kmax and Kmin values. After that, UCVA, BCVA, and Kmax remained stable during all the follow-up period of the study, while Kmin remained stable until 5 years after surgery, but increased afterwards. CTTP did not significantly changed with ICRS implantation.

Abreu et al previously reported the 5-years outcomes of ICRS implantation in our center. Comparing month 6 to 12 after surgery with preoperative values, there was an improvement in UCVA, BCVA, Kmax, and Kmin. At the end of follow-up these values remained stable.11 Of note, in the present analysis fewer patients were evaluated, compared to the study by Abreu et al, since some patients were lost to follow-up and were, therefore, excluded.

Few other studies evaluated the outcomes of ICRS implantation in pediatric patients. Ertan et al compared ICRS implantation in different age groups: 13 to 19 years old, 20 to 35 and 35 to 56 years old. There was an improvement in both uncorrected and spectacle BCVA, and keratometry values one year after surgery in each group, without statistically significant differences between groups. Hence, the authors concluded that ICRS implantation was safe and efficient in all age groups. [12].

Alfonso et al evaluated the long-term outcomes of ICRS implantation in pediatric patients. After 6 months of implantation of Ferrara® (AJL Ophthalmic, Vitoria-Gasteiz, Spain) ICRS, there was an improvement in the UCVA, as well as in keratometric values. There was also an important increase in the percentage of eyes with a BCVA inferior to 0.1 logMAR (from 39.0% to 73.7%). The 12-, 36- and 60-month follow-ups demonstrated that this improvement in the visual and keratometric parameters were stable over time. Taking this into consideration, the authors concluded that Ferrara® ICRS are a safe and effective procedure for visual restauration in pediatric patients with keratoconus. [13].

Ferrara et al evaluated the medium-term outcomes (6 to 81 months) of Ferrara® ICRS implantation in children with keratoconus. The authors verified that there was as an improvement in mean UCVA and BCVA after surgery, and a reduction in Kmax and Kmin one month after surgery. Between the first month and the second year of follow-up there were no changes in UCVA, BCVA and Kmin values but there was a progressive increase of Kmax. One patient needed cross-linking and one patient needed a lamellar keratoplasty due to progressive steepening despite ICRS implantation. [14].

Mendéz et al evaluated 26 eyes of pediatric patients submitted to ICRS implantation. Ten eyes were submitted only to ICRS implantation and 16 eyes to ICRS implantation followed by cross-linking. The authors reported an increase in BCVA and central corneal thickness, and a decrease in Kmax and Kmin in both groups. Additionally, there was as an increase in UCVA in the ICRS followed by cross-linking group. On turn, there was a decrease in UCVA in the ICRS alone group. Despite this, the authors did not perform statistical tests to compare preoperative and postoperative values and mean/median values were directly compared. [15].

Abdelmassih et al evaluated the outcomes of ICRS implantation in 17 eyes, followed by cross-linking after 1 month. At the 6-month follow-up there was a significant improvement in UCVA and BCVA, and a decrease in the keratometry values. At the 4-year follow-up the only significant change compared to the 6-month visit was an increase in UCVA. The authors concluded that ICRS implantation followed by cross-linking is a safe and effective procedure for visual rehabilitation of pediatric keratoconus with poor BCVA or anisometropia. [16].

The results of our study are in line with those found by other authors, showing that ICRS seem to improve both BCVA and UCVA, as well as leading to a decrease of Kmax and Kmin values.

Our study has some limitations, in particular the small number of eyes included and its retrospective nature. Additionally, surgeries were performed using a manual technique. Monteiro et al showed that the rate of complications with Femtosecond LASER, including late ICRS spontaneous extrusion, is inferior to that found with a manual technique. [17]. Two of our patients required explantation of at least one of the ICRS in the first two years after surgery, which may be related to surgical technique, namely insufficient depth of ICRS implantation. With the current use of the Femtosecond LASER, the rate of ICRS extrusion would probably be lower.

All our patients had progressive keratoconus but, at the time of ICRS implantation, cross-linking was not yet available in our center. Furthermore, the level of evidence showing the efficacy and safety of crosslinking to halt keratoconus progression was lower than it is today.

Lastly, Intacs® and Intacs SK® were implanted, and the nomogram used considered only the refractive spherical equivalent. Currently, ICRS implantation nomograms are based in a wider range of information that include cone phenotype, refractive and topographic astigmatism, and higher order aberrations, namely, the coma. [18]. Therefore, outcomes of ICRS implantation based on more recent nomograms, would probably allow better clinical outcomes.

Regardless of these limitations, knowing the long-term outcome of pediatric patients with progressive keratoconus implanted with ICRS is of major importance. Despite the good results in the first years after surgery, the number of patients requiring ICRS explantation increased with time, with most of the cases happening more than 9 years after implantation. Furthermore, after 5 years there was an increase in the Kmin value and, therefore, the benefits of ICRS implantation may decrease overtime. This objective new data was not yet known due to lower follow-up times of all currently published studies.

In conclusion, although cross-linking is the current gold-standard treatment for progressive keratoconus, it does not seem to provide a significant improvement in visual acuity. [5]. Hence, ICRS implantation may be considered as an option to improve vision and to postpone the need for corneal transplantation, either alone or in combination with cross-linking. The rate of ICRS extrusion and the need for additional treatments, such as DALK, increased overtime, possibly making long-term results of ICRS implantation less favorable in pediatric patients with progressive keratoconus. Despite this, there was a subgroup of patients with sustained good results, even after 10 years of follow-up. Adding cross-linking to ICRS may further improve the outcomes. Hence, further long-term studies, including more patients, with ICRS implanted with Femtosecond LASER, based on more recent nomograms, and studies that include the use of cross-linking as a rescue treatment for eyes that continue progressing despite ICRS implantation, are necessary to better understand the role of ICRS in pediatric patients with keratoconus.

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Abbreviations. *BCVA – Best-corrected visual acuity; CTTP – Corneal thickness in the thinnest point; ICRS – Intrastromal corneal ring segments; Kmax – Maximum keratometry; Kmin – Minimum keratometry; UCVA – Uncorrected visual acuity*

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