Effectiveness of Intrastromal Corneal Ring Implantation in the Treatment of Adult Patients With Keratoconus: A Systematic Review

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ABSTRACT

PURPOSE: To evaluate the available evidence on the effectiveness of intrastromal corneal rings (ICRs) in the treatment of adults with keratoconus.

METHODS: A systematic review of electronic databases was completed through July 30, 2017. All primary research articles in which adults with keratoconus were treated with ICRs were included. Two independent reviewers assessed methodological quality and classified the studies into high, low, or undefined risk of bias. The measured variables assessed were visual acuity, refraction, keratometry, ring type, and complications.

RESULTS: The initial search yielded 442 scientific articles, 62 articles were read extensively, and 18 articles were assessed for eligibility and included for statistical analysis and quality assessment. A total of 1,325 eyes were analyzed, and the results were evaluated preoperatively and at 12 months of follow-up. Uncorrected distance visual acuity (UDVA) improved 0.23 ± 0.28 logMAR and corrected distance visual acuity (CDVA) improved 0.06 ± 0.21 logMAR. Sphere improved 2.81 ± 1.54 diopters (D), cylinder improved 1.49 ± 0.83 D, and mean keratometry improved 3.41 ± 2.13 D within 12 months of follow-up. ICR implantation combined with corneal crosslinking improved UDVA, refraction, and keratometry to a greater degree than ICR implantation alone.

CONCLUSIONS: The studies analyzed demonstrate refractive and visual improvement of patients treated with the ICR implantation technique. However, description of the methodological process necessary to evaluate the bias effectively is insufficient.

[*J Refract Surg*. 2019;35(3):191-200.]

Intrastromal corneal ring (ICR) implantation was introduced initially to correct low myopia and first reported in normal myopic eyes in 1995.[1] Studies provided evidence of improvement in visual acuity with and without correction. The same group observed that ring placement flattened the central cornea and regularized tissue asymmetry, thereby reducing keratometry and improving refractive error and visual acuity. Accordingly, they successfully implanted the first ICR in patients with keratoconus in June 1997. Other techniques, such as the excimer laser, replaced the ICR implantation as a primary indication for the treatment of the myopia. ICRs were approved by the U.S. Food and Drug Administration for use in humans in 1999 for patients with myopia and in July 2004 for patients with keratoconus.[2]

Likewise, similar ICRs such as the Ferrara Ring (AJL Ophthalmic, Miñano, Spain), Keraring (Mediphacos, Belo Horizonte, Brazil), INTACS SK (Addition Technology, Inc., Santa Clara, CA), and MyoRing (DIOPTIX, Linz, Austria) are widely used in several countries around the world but are not yet approved by the U.S. Food and Drug Administration. The primary difference between these devices is that the optical

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Submitted: May 21, 2018; Accepted: January 7, 2019

The authors have no financial or proprietary interest in the materials presented herein.

The authors thank Jose Chauca, PhD, for helping with the statistical analysis and Carmen Maldonado, MSc, as the study coordinator.

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doi:10.3928/1081597X-20190109-02

zone is approximately 7 mm in the INTACS and 4.5 to 5 mm in the Ferrara and Keraring devices. The latter have a triangular shape, whereas the INTACS has a hexagonal shape and the INTACS SK is elliptical.[3]

To date, there is no publication available that systematizes the results of the information published so far regarding ICR implantation in patients with keratoconus. On the other hand, although there is much available evidence regarding the visual, refractive, and topographic results in patients with keratoconus undergoing ICR implantation, many of the publications are clinical cases or case series without a comparison group, which contribute little to defining the effectiveness of these devices in the treatment of the disease.

We performed a systematic review to evaluate the effectiveness of ICR treatment compared to other procedures and techniques (eg, corneal cross-linking [CXL], gas-permeable contact lenses, photorefractive surgery, and corneal transplantation) to improve visual outcomes in adults diagnosed as having keratoconus. The primary objective of the study was to consolidate the scientific evidence that proves the effectiveness of the treatment in relation to visual acuity and refraction in adults with keratoconus and to compare the outcomes of these treatments with those of other treatment modalities.

PATIENTS AND METHODS

Design and Registration

This was a systematic review of primary research articles published in scientific databases, developed under an internationally recommended methodology, to generate a comprehensive, standardized, reliable, and replicable summary of the best evidence available thus far. The protocol was presented to and approved by the Scientific Ethics Committee of the Instituto de Ojos Oftalmosalud, Lima, Peru.

Electronic Databases

The search was conducted in: Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Register of the Eyes and Vision Group); PubMed according to MESH terms and clinical queries; Latin American and Caribbean Health Sciences Literature Database (LILACS); Scientific Electronic Library Online (www.scielo.org); Scopus; EMBASE; and Epistemonikos (www.epistemonikos.org). Bibliographical references of reviews or articles published to date related to the topic were also reviewed.

Search Strategy

The search key words that were used in the databases were: "corneal ring," "intrastromal corneal ring," "INTACS," "MyoRing," "Keraring," "Ferrara Ring," and "Intracorneal ring." There was no filter by date of publication. The search was done systematically up to July 30, 2017. If no MESH terms were found for intrastromal rings in the PubMed database, the search strategy was as follows: [All Fields] OR "intrastromal ring" [All Fields] OR " corneal ring" [All Fields] OR "myoring" [All Fields] OR "keraring" [All Fields] OR "intacs" [All Fields]. When the search did not yield adequate results, a broader search was performed using clinical queries with the key words "corneal ring" without any other filter.

Inclusion Criteria

Type of publication was primary research articles published in scientific databases. Type of studies was prospective and retrospective design studies that had a comparator group based on another type of treatment or without treatment. Type of study participants was articles whose study population was adult patients with keratoconus. Type of result was articles that analyzed any of the following main and secondary results: visual acuity, topography, refraction, implant depth, tunneling or channel placement, corneal thickness, or contact lens tolerance. Type of intervention was articles that evaluated the implantation of ICRs in a unique way or combined with some other treatment (CXL, photorefractive keratectomy, or contact lenses). Sample size was 30 or more eyes studied by article. Articles without a year of publication filter and in any language were included.

The analysis of the type of intervention was performed separately for those eyes that were only implanted with an ICR and those that were combined procedures, so we eliminated the confounding effect by separating the analysis by blocks of treatment that are explained in the results and statistical methodology.

Exclusion Criteria

Exclusion criteria were studies of case series without a comparison group, clinical cases, case–control, transverse, literature reviews, letters to the editor, protocols, and experimental studies performed in animals or in vitro, studies that evaluated corneal ectasia from other causes, and articles that had summaries unrelated to the topic being studied.

Primary Outcomes

The primary outcome was improved refraction and/or visual acuity. Secondary outcomes were: preoperative visual acuity without correction (pre-UDVA), measured in logMAR; preoperative visual acuity with correction (pre-CDVA), measured in logMAR; postoperative visual acuity without correction (post-UDVA),

measured in logMAR; postoperative visual acuity with correction (post-CDVA), measured in logMAR; preoperative refraction, measured in sphere, cylinder, and axis; postoperative refraction, measured in sphere, cylinder, and axis; and improved refraction, measured in sphere, cylinder, and axis.

Other Variables

During the data extraction process, the variables to be studied were age; sex: female or male; keratometry, measured in microns; depth of the implant, measured in micrometers; intrastromal ring type, identified as: Keraring, Myoring, Ferrara ring, INTACS, or INTAC SK; follow-up time, measured in months; complications: infectious keratitis, corneal haze, corneal scars, halos, corneal epithelial defects, diplopia, vision fluctuation, implant migration, canal defect, or neovascularization; channel dissection method, either mechanical or femtosecond laser; the position of the intrastromal ring, measured in degrees; optical zone, measured in millimeters; length of the arc, measured in millimeters; and combined procedures (CXL, intraocular lens implant, and photorefractive keratectomy).

Data Extraction Process

Two independent reviewers assessed the titles and abstracts of all literature found online, categorized search results, and selected potentially eligible articles for review. Duplicate and non-mainstream studies were excluded from the initial search. The complete texts of the selected articles were extracted, and a detailed study of each of the articles was carried out.

Two authors independently reviewed the complete articles using an Excel database (Microsoft Corporation, Redmond, WA) to enter the results of the variables to be studied in each of the articles. The same two reviewers extracted data from each article and analyzed the methodological quality and characteristics of the articles included in the review.

For dichotomous results, the number of participants for each intervention and the number of participants who experienced the event were collected. For continuous data, the mean and standard deviation were collected and the median and the interquartile range of the data were skewed for each study.

Evaluation of Methodological Quality

The risk of bias was measured using the methodology described in Chapter 8 of the Cochrane Collaboration Guidelines for Systematic Reviews of Interventions.

Reviewers entered the evaluation of the methodological quality of each of the articles into an Excel database independently.

For both main and secondary results, significant differences were reported with a 95% confidence interval.

The following parameters were considered for assessing the risk of bias in clinical trials: selection of bias (generation by random sequences or adequacy of allocation concealment); bias management (masking of participants and study staff); detection of bias (masking of outcome assessors); attrition bias (incomplete follow-up, causes of data loss); reporting bias (report of selective outcomes); and other types of biases such as financing and confusion bias.

Each study was evaluated for each parameter and described it as low risk, high risk, or non-evaluable risk (in the case of articles with insufficient information for making a judgment).

For the randomization method, the generation of randomized sequences with computational generators of random numbers, tables with random numbers, closed envelopes, or shuffled letters was considered low risk. For concealment of assignment, central concealment or numbered sealed in opaque wrappings was considered low risk. For the masking of the participants, staff, and results of the evaluation, the description was carefully searched in each of the articles. Regarding follow-up of the participants, we assessed homogeneity among the groups and whether the analysis was performed according to intention to treat. The selective report was evaluated in relation to the inclusiveness of the results and analysis. Confusion was assessed in relation to homogeneity between groups, in cases where differences from the comparison group were significant.

Prospective and retrospective cohort studies, comparative studies, and cases series with comparison groups did not take into account group randomization and masking in the assessment of bias.

A third reviewer was included to define and agree on the categorization, for adjudication of a difference between the evaluations of each of the primary reviewers.

Management of Heterogeneity

We evaluated the clinical, methodological, and statistical heterogeneity of the studies included in the research. The evaluation was based on the characteristics of the participants, the intervention, and the results of the included studies.

It was not feasible to condense the results into a true meta-analysis for several reasons. Although all studies analyzed had a comparison group, we noted that all selected articles implanted ICRs in the two groups, and the variable analyzed was what modified the result, so there was no control group without treatment.

When trying to determine a correlation of the variables between before and after implantation of the ICR of 0.7 with the Fixed-Effects Model, the heterogeneity of the sample presented was high. Therefore, we decided to describe the results independently for each variable to be analyzed. It was not possible to perform a meta-analysis because the sample was too heterogeneous.

RESULTS

Descriptive Analysis

The initial search yielded 442 scientific articles (**Figure A**, available in the online version of this article). Thirty-eight articles were excluded and 342 articles were not relevant to the subject to be studied (post-LASIK ectasias, letters to the editor, or reviews). Sixty-two articles were read extensively. The analysis found that 39 articles did not meet the inclusion criteria. Among them, 25 were case reports, 10 had no comparison group, and 4 were literature reviews. A total of 23 articles were assessed for eligibility, and 5 full-text articles were excluded due a scarce sample and different topic analyzed. Finally, 18 studies were selected for statistical, bias, and results analysis.

Of the 18 articles selected, 5 articles were randomized clinical trials, 4 articles were retrospective cohorts, and 9 articles were comparative clinical studies. A total of 1,325 eyes were analyzed, and the results were evaluated preoperatively and at 12 months of follow-up (**Tables 1-3**). Eight selected articles included the use of combination therapy with CXL. Therefore, they were analyzed separately to avoid affecting the results. One article compared the outcomes of deep anterior lamellar keratoplasty and ICRs.[4]

Inclusion Criteria and Preoperative Analysis for ICR Selection

All analyzed articles used clear visual axis without scars and intolerance to contact lenses as inclusion criteria. ICRs were used for keratoconus with a mean steeper keratometry range from 47.06 to 59.24 diopters (D). Only one article used a steeper keratometry with a cut-off of 65.00 D as an inclusion criterion.[4]

The thickness was measured ultrasonically in 2 articles,[5,6] the authors used anterior segment optical coherence tomography to measure the depth of implantation in 2 articles,[5,6] and measurements of the corneal topography were done with the Orbscan II,[1,4,7-12] Oculus Pentacam,[1,5,6,13-15] ODP-scan ARK-1000 Nidek,[16] Schwind Corneal Wavefront Analyzer,[17] and Intralase FS (Abbott Medical Optics).[12,18] Ferenczy et al.[19] did not mention the topographer used for the study. Nearly all (61.1%) of the articles divided the sample according to the Amsler–Krumeich classification; the other studies[1,6,11,13,14,18,19] did not mention it. Four articles (36.3%) included keratoconus grades 1 to 4,[7,8,14,15] 1 study (9.09%) included grades 1 to 2, 2 articles (18.18%) included grades 1 to 3,[9,12] 3 articles (27.3%) included only grades 2 and 3,[5,10,16] and 1 article (9.09%) included keratoconus grades 3 and 4.[4]

Analysis With ICR Implantation Alone

The improvement of visual acuity was 0.23 ± 0.28 logMAR without correction (UDVA) and 0.06 ± 0.21 logMAR with correction (CDVA) at 12 months of follow-up. With regard to refraction, the sphere improved 2.81 ± 1.54 D and the cylinder improved 1.49 ± 0.83 D by 12 months of follow-up. Preoperative mean keratometry demonstrated a mean flattening of 3.41 ± 2.13 D 1 year after ICR implantation.

Analysis in Combined Procedures (ICR and CXL)

When analyzing the articles using ICRs combined with CXL, we noted that UDVA improved 0.12 logMAR at 12 months of follow-up, CDVA worsened 0.03 logMAR at 12 months of follow-up, but the mean sphere and cylinder component improved 3.03 ± 1.99 and 1.99 ± 0.96 D, respectively, at 12 months of follow-up. Keratometry improved 4.31 ± 2.62 D at 12 months of follow-up. Thus, UDVA, refraction, and keratometry improved to a greater degree than if only the ICR procedure was used.

Complications

The primary complications in the ICR group were white deposits (57 [5.75%]), epithelial defects (56 [5.65%]), extrusion (21 [2.11%]), decentration (14 [1.41%]), segment migration (6 [0.6%]), and halos and glare (6 [0.6%]). In the ICR and CXL group, the main complications were edema (17 [5.08%]), extrusion (2 [0.59%]), perforation (2 [0.59%]), and corneal melting (1 [0.29%]) (**Tables 4-5**).

Manual Versus Femtosecond Laser Technique

Mean UDVA, CDVA, and keratometry improved 0.03 logMAR, 0.05 logMAR, and 3.55 D, respectively, with the manual technique and 0.36 logMAR, 0.07 logMAR, and 3.32 D, respectively, with the femtosecond laser technique. This indicated better improvement in UDVA with the femtosecond laser technique, but this was not statistically significant.

Different Types of ICRs

All types of ICRs were associated with an improvement in visual acuity and spherical and cylindrical component; however, the ring that appeared to give the most robust spherical component improvement

TABLE 1
Clinical Trial Studies Included in Qualitative Synthesis

Clinical Trial	Year	Journal	Country	Participants	Intervention	Comparator Group	Eyes	Main Results
Jabbarvand	2014	Cornea	Iran	Adults with keratoconus	250 µm depth	300 µm depth	42	No significant differences in visual, refractive, aberrometric, keratometric, and biomechanical corneal changes between the two depths of the implant.
Kubaloglu	2010	J Cataract Refract Surg	Turkey	Adults with keratoconus	Keraring: femtosecond laser technique	Keraring: manual technique	100	Visual and refractive results are comparables between femtosecond and manual technique, although the femtosecond method is faster, easier, and more comfortable for the patient and surgeon and accurate in depth.
Renesto	2012	Am J Ophthalmol	Brazil	Adults with keratoconus	CXL + ICR	Riboflavin + ICR	39	No significant differences in visual acuity and refraction. CXL does not appear to increase the effect of ICR after its insertion.
Al-Tuwairqi	2016	Int Ophthalmol	Saudi Arabia	Adults with keratoconus	Keraring	MyoRing	44	Slightly better visual acuity in MyoRing group.
Coskunseven	2009	J Cataract Refract Surg	Turkey	Adults with keratoconus	CXL then ICR	ICR then CXL	48	ICR followed by CXL results in greater improvement in keratoconus than CXL followed by ICRs (improved CDVA and decreased cylinder).

CXL = corneal cross-linking; ICR = intrastromal corneal ring segment implantation; CDVA = corrected distance visual acuity
The Keraring is manufactured by Mediphacos, Belo Horizonte, Brazil, and the MyoRing is manufactured by DIOPTIX, Linz, Austria.

TABLE 2
Cohort Studies Included in Qualitative Synthesis

Cohort Study	Year	Journal	Country	Participants	Intervention	Comparator Group	Eyes	Main Results
Kubaloglu	2010	J Cataract Refract Surg	Turkey	Adults with keratoconus	Keraring ICR	INTACS ICR	168	Both models are effective and safe. The increase of CDVA and UDVA and the decrease of SE and K max was greater after Keraring implantation.
Ferenczy	2015	Arq Bras Oftalmol	Brazil	Adults with keratoconus	ICR	ICR + CXL	32	Significant improvement of visual acuity and spherical component values, decrease of cone apex curvature in topographic analysis, and decrease of postoperative corrected diopters.
Liu	2015	Int J Ophthalmol	China	Adults with keratoconus	Ferrara Ring + CXL	CXL + Ferrara Ring	41	No significant differences between groups using different sequences and times.
Bikvoba	2018	Int Ophthalmol	Russia	Adults with keratoconus	MyoRing	MyoRing + CXL	78	Both techniques can be effective for treating keratoconus and are safe and effective for moderate and severe degrees.

ICR = intrastromal corneal ring segment implantation; CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity; SE = spherical equivalent; K max = maximum keratometry; CXL = corneal cross-linking
The Keraring is manufactured by Mediphacos, Belo Horizonte, Brazil, the INTACS SK is manufactured by Addition Technology, Inc., Santa Clara, CA, the Ferrara Ring is manufactured by AJL Ophthalmic, Miñano, Spain, and the MyoRing is manufactured by DIOPTIX, Linz, Austria.

TABLE 3

Comparative and Cases Series Studies Included in the Qualitative Synthesis

Study	Year	Journal	Country	Participants	Intervention	Comparator Group	Eyes	Main Results
Kaya	2011	J Refract Surg	Turkey	Adults with keratoconus	INTACS	Ferrara Ring	33	Better outcomes with Ferrara Ring compared with INTACS.
Kapasi	2012	Can J Ophthalmol	Canada	Adults with keratoconus	Central cone + ICR	Eccentric cone + ICR	31	The visual and refractive results of the ICR implant in central and eccentric cones are comparable to each other, except for the UDVA.
Haddad	2012	J Cataract Refract Surg	Lebanon	Adults with keratoconus	INTACS SK	Keraring S16	173	Both implantation significantly improved visual acuity, refraction, topography, and coma at 1 year. Both procedures were safe and yielded comparable results.
Çakir	2013	Eur J Ophthalmol	Turkey	Adults with keratoconus	ICR	ICR + CXL	166	Both resulted in favorable outcomes in keratoconus in the aspects of visual acuity, spherical and cylindrical errors, and mean keratometry values.
Al-Muammar	2015	Middle East Afr J Ophthalmol	Saudi Arabia	Adults with keratoconus	INTACS	INTACS SK	34	INTACS and INTACS SK were comparable.
Hashemian	2014	J Ophthalmic Vis Res	Iran	Adults with keratoconus	INTACS	INTACS SK	33	INTACS and INTACS SK were comparable.
Piñero	2009	Ophthalmology	Spain, Turkey	Adults with keratoconus	Mechanical procedure	Femtosecond-assisted procedure	146	No significant differences in refractive and visual outcomes.
Yeung	2013	J Cataract Refract Surg	Canada	Adults with progressive keratoconus	Single ICR combined with CXL	Paired ring segment combined with CXL	85	Both ICRs placed in combination with CXL reduced corneal astigmatism, improved UDVA, and was a safe and effective treatment for progressive keratoconus.
Özertürk	2012	J Cataract Refract Surg	Turkey	Adults with keratoconus	DALK	Femtosecond ICR (Keraring segments) implantation	67	ICR implantation is a safe and effective procedure for the management of advanced keratoconus without central corneal scarring.

ICR = intrastromal corneal ring segment; UDVA = uncorrected distance visual acuity; CXL = corneal cross-linking; DALK = deep anterior lamellar keratoplasty
The Keraring is manufactured by Mediphacos, Belo Horizonte, Brazil, the INTACS SK is manufactured by Addition Technology, Inc., Santa Clara, CA, and the Ferrara Ring is manufactured by AJL Ophthalmic, Miñano, Spain.

TABLE 4
Complications of Each Study

Study	N	Complications
ICR only		
Jabbarvand, 2014	42	Halos and glare sensation in all patients at first visit; after 1 year, 1 patient maintained symptoms.
Kubaloglu, 2010	100	Anterior corneal perforation: 1 eye in mechanical group; superficial segment placement: 1 eye in mechanical group; segment extrusion: 1 eye in mechanical group; segment migration: 1 eye in femtosecond group; limited epithelial defects: 22 eyes in mechanical group and 7 eyes in femtosecond group; white deposits: 17 eyes in mechanical group and 19 eyes in femtosecond group.
Al-Tuwairqi, 2016	44	MyoRing group: segment displacement (1 eye), superficial movement of the segment (1 eye), and infiltrative keratitis (1 eye).
Ferenczy, 2015	22	None
Kubaloglu, 2010	168	Anterior perforation: 1 eye in mechanical group; extrusion: 4 eyes in mechanical group and 1 eye in femtosecond group; descentration: 4 eyes in mechanical group and 3 eyes in femtosecond group; shallow placement: 1 eye in mechanical group.
Kapasi, 2012	31	None
Kaya, 2011	33	Neovascularization (1 eye).
Liu, 2015	25	Corneal transplant (1 eye) due to photophobia and poor visual acuity. Extrusion (4 eyes), corneal melting (1 eye), infectious keratitis (1 eye).
Piñero, 2009	146	Explantation: 12 eyes of the mechanical group and 11 eyes of the femtosecond group. Reasons: extrusion (8 eyes), corneal melting (3 eyes), corneal neovascularization (2 eyes), and very poor visual outcomes. Infectious keratitis 1 eye at 6 months postoperatively.
Haddad, 2012	173	Perioperative 6 eyes, deep implantation (2 eyes), breaks of segments (3 eyes), recurrent epithelial erosions at incision (1 eye), and infiltrate suture side (1 eye).
Hashemian, 2014	33	Not described.
Özertürk, 2012	30	Limited epithelial defects in 27 eyes; sterile white deposits in the corneal channel in 19 eyes; segment extrusion: 1 eye.
Bikbova, 2018	41	5 eyes reported night vision problems and glare.
Çakir, 2013	69	Extrusion: 2 eyes.
Al-Muammar, 2015	34	Not described
ICR + CXL		
Renesto, 2012	39	Anterior chamber perforation (2 eyes; riboflavin eye drops group).
Coskunseven, 2009	48	8 eyes with slight subepithelial and stromal edema with cotton-like ring-shaped stromal opacities 1 month after CXL treatment.
Ferenczy, 2015	10	None
Liu, 2015	16	Extrusion: 1 eye, corneal melting: 1 eye.
Bikbova, 2018	39	Slight stromal edema: 9 eyes.
Çakir, 2013	97	Extrusion: 1 eye; transient corneal haze in all eyes.
Yeung, 2013	85	None

ICR = intrastromal corneal ring segment implantation; CXL = corneal cross-linking
The MyoRing is manufactured by DIOPTIX, Linz, Austria.

was MyoRing with a mean reduction of 6.26 D and the INTACS SK with a mean reduction of the cylindrical component of 4.39 D at 12 months of follow-up. Regarding keratometry, the greatest improvement was achieved with the MyoRing with a mean flattening of 7.78 D at 12 months of follow-up. These results were analyzed in 15 articles that described the type of device used without CXL (N = 725), with a total of 5 studies for KeraRing,[4,7,8,15,17] (50.06%), 2 studies for MyoRing[16,17] (8.13%), 3 studies for INTACS[8,10,11,20] (16.1%), 2 studies for Ferrara Ring[10,12] (11.86%), and 3 studies for INTACS SK[11,15,20] (13.79%).

Bias Analysis

The bias measurement was performed by two researchers and the results are summarized in **Figure B** (available in the online version of this article). In general, we found many shortcomings in the pub-

TABLE 5
Complications

Complication	ICR (n = 991 Eyes)	ICR + CXL (n = 334 Eyes)
Halo and glare	6 (0.6%)	0
Migration	6 (0.6%)	0
Extrusion	21 (2.11%)	2 (0.59%)
Epithelial defect	56 (5.65%)	0
White deposit	57 (5.75%)	0
Infectious keratitis	3 (0.3%)	0
Perforation	2 (0.2%)	2 (0.59%)
Neovascularization	3 (0.3%)	0
Poor visual acuity	1 (0.1%)	0
Corneal melting	4 (0.4%)	1 (0.29%)
Descentration	14 (1.41%)	0
Recurrent epithelial erosion	1 (0.1%)	0
Break of segments	3 (0.3%)	0
Edema	0	17 (5.08%)
Progression	1 (0.1%)	0

ICR = intrastromal corneal ring implantation; CXL = corneal cross-linking

lished literature because large amounts of data were not mentioned in the methodology. Clinical trial studies should describe the methodology employed to obtain their results. Only one article, published by Al-Tuwairqui et al.,[17] showed a low risk of methodological bias in all of the variables analyzed.

Only randomized clinical trials analyzed all variables with bias analysis.[5-7,9,17] Cohort studies and clinical studies with a comparison group were not randomized; as such, these studies were based on incomplete outcomes data, selective reporting, and other kinds of bias.

DISCUSSION

In the information provided by the articles selected, 1,325 eyes had implanted ICRs. The inclusion criteria used were clear visual axis without scars and intolerance to contact lenses, and the majority of the articles divided the sample according to the Amsler–Krumeich classification. Keratoconus cases grades 1 to 4 were treated with ICR implantation.

Ring segments may be implanted using manual or femtosecond laser–assisted techniques. It is believed that the creation of the mechanical tunnel is more complex and dependent on the skill of the surgeon, whereas the technique with the femtosecond laser is faster and more precise and, hence, more reproducible.[7] In our systematic selection, 3 articles[5,9,18] were excluded for this analysis because both groups received ICR implantation associated with CXL. Thus, 15 studies had at least one ICR implantation alone group between them: 8 articles (53.3%) implanted ICRs only with the femtosecond laser technique[4,6,10,12,14,15,17,19]; 3 articles (20%) compared the implant between the manual and femtosecond laser–assisted techniques[1,7,8]; and 4 (26.6%) articles implanted ICRs only with the manual technique.[11,13,16,20] Those articles that compared the techniques found no statistically significant differences between them.

Several studies have evaluated the combination of CXL treatments and ICR implantation with good results.[12,13,16,19,21] To date, however, few studies evaluating visual and refractive outcomes have been published in relation to the depth of the ICR implant.[6] Among our selection, there were 5 articles (35,71%) in which the ICR implant techniques and CXL were compared.[5,9,13,16,19] Liu et al.[13] performed a retrospective cohort analysis to evaluate the results of ICR implantation followed by CXL versus CXL followed by ICR implantation and did not find significant differences between the sequences. Coskunseven et al.[9] compared two treatment groups with different sequences. The group with ICR implantation followed by CXL demonstrated statistically significant improvement, overall higher increase in CDVA, and greater decrease in cylinder than the group with CXL first and then ICR implantation. No statistical difference between groups was found in terms of UDVA, spherical equivalent, or mean keratometry. Ferenczy et al.[19] performed a retrospective cohort analysis of ICR implantation only compared to ICR implantation plus CXL at a later date and found no significant differences between the two techniques in relation to visual acuity. Nevertheless, this study concluded that the ICR implant did not ensure cessation of the disease. Renesto et al.[5] found no significant differences in UDVA, CDVA, refractive results, spherical component, cylindrical component, and mean keratometry between traditional CXL with ICR implantation at a later time compared with riboflavin drops followed by ICR implantation. There was no information related to disease progression. Finally, Bikbova et al.[16] performed a cohort retrospective study between MyoRing alone compared to MyoRing followed by CXL and showed that CXL stabilized the disease and produced better keratometric results. Better CDVA results were obtained with the ICR implant alone.

The most robust sphere component improvement was with MyoRing devices with a mean of 6.26 D. These results could be justified because MyoRing corresponds to a continuous ring of 360 degrees, so the power of flattening is greater in the entire corneal surface.

Complications are rare but do occur. Intraoperative complications are mainly linked to the construction of the tunnel in manual techniques. The most frequent are decentration of the segments, inadequate depth of the tunnel, and asymmetry of the segments. Postoperative complications include ring segment extrusion, corneal neovascularization, corneal haze, segment migration, corneal melting, and infectious keratitis, among others.[22,23] Other less common complications include persistent inflammation, fluctuating vision, photophobia, and pain in the absence of infection.[7,23] Our search yielded 16 articles (88.8%) that referred to complications in their results or discussion. No complications during the follow-up period were noted in 2 articles in the ICRS implantation alone group[14,19] and 2 articles in the CXL group.[18,19] The primary complications were white deposits (5.75%) and epithelial defects (5.65%) in the ICR group alone and edema (5.08%), perforation (0.59%) and extrusion (0.59%), in the CXL group.

Özertürk et al.[4] compared deep anterior lamellar keratoplasty versus ICR implantation in advanced keratoconus (Amsler–Krumeich classification III and IV) and concluded both treatments were safe and effective for the management of advanced keratoconus, but the visual impact of ICR implantation seemed to be less significant than that achieved with deep anterior lamellar keratoplasty ($P = .02$ between groups for UDVA).

In the analyzed literature, significant refractive and visual improvement of eyes treated with ICR implantation were observed. Although a variety of complications are described both intraoperatively and postoperatively, the most frequent did not exceed 10%. Regarding the combined procedures with CXL compared with ICR alone, there was significant refractive, visual, and topographical improvement in the combined procedures. However, there is insufficient description of the methodological process necessary to evaluate the bias effectively.

AUTHOR CONTRIBUTIONS

Study concept and design (LI, MJM, JAMS, MAH); data collection (JAMS); analysis and interpretation of data (LI, JAMS); writing the manuscript (LI, JAMS, MAH); critical revision of the manuscript (LI, MJM, JAMS, MAH); statistical expertise (MAH); administrative, technical, or material support (JAMS); supervision (LI, MJM, MAH)

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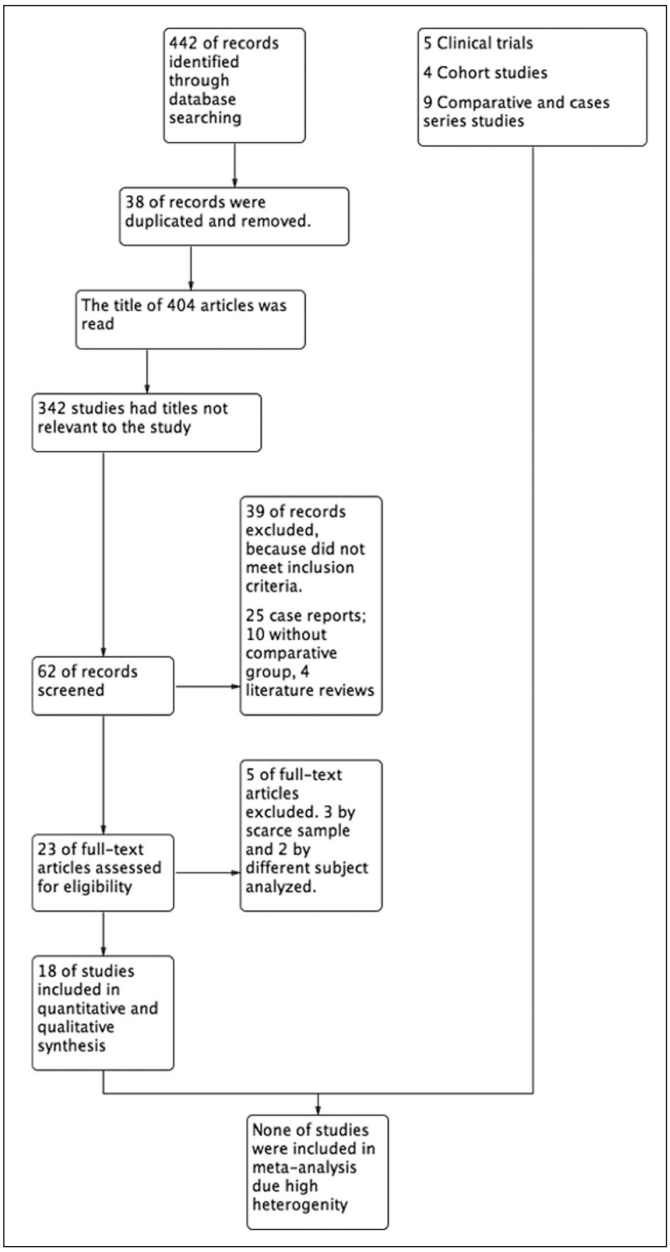

Figure A. Study flow diagram.

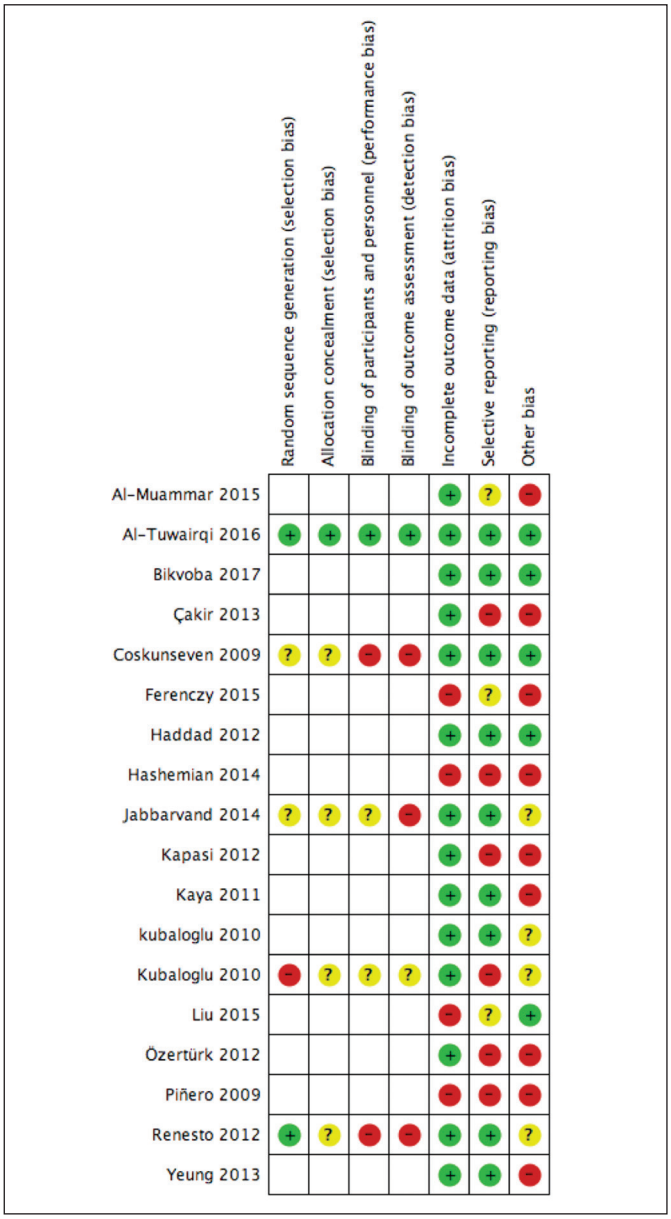

Figure B. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.