Title

Small-Aperture Intracorneal Inlay Implantation in Emmetropic Presbyopic Patients: A Systematic Review

Running Title

KAMRA: A Systematic Review

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Abstract

Small-aperture corneal inlays, commonly known as KAMRA, are tiny optical devices inserted in the corneal stroma aiming to gain near vision in patients with presbyopia. The purpose of this study was to systematically review case series of small-aperture corneal inlays performed in presbyopic emmetropic patients and to evaluate the visual outcomes of this procedure. This systematic review included 18 articles published between 2011 and 2018, overall studying 2724 eyes from 2691 participants. The mean longest follow-up was 19 months. Results showed that 78.5% of eyes reported an uncorrected near visual acuity of 20/32 or better and 90.50% of eyes achieved an uncorrected distance visual acuity of 20/25 or better. All patients experienced an improvement in uncorrected near visual acuity with a patient satisfaction ranging between 60% and 90%. The highlighted complications were keratocyte activation leading to corneal stromal haze, epithelial growth, iron deposits and poor distance visual acuity. Explantation was carried out in 101 eyes (3.7%) due to distance vision blurriness, development of epithelial microcysts, incorrect implant placement or hyperopic shift changes. KAMRA demonstrated high efficacy. However, safety and satisfaction rates remain unclear. Despite the low explantation rates reported in the literature, some complications were permanent. The results and conclusions should be taken with caution due to the conflict of interest stated in the reviewed articles.

Keywords

Small-aperture corneal inlay; inlay; KAMRA; presbyopia

Introduction

Presbyopia is the most common refractive error and its prevalence continues to increase every year.[1] Corneal inlay implantation devices are placed in the cornea in a monocular fashion, improving near and intermediate visual acuity while maintaining distance vision.[2] They are placed in a stromal pocket that is previously created using either femtosecond laser or mechanically using a microkeratome. This surgical procedure can be performed by either varying the corneal refractive index [3,4] or by modifying the corneal curvature [3,4]. However, the small-aperture intracorneal inlay (KAMRA™, AcuFocus Inc., Irvine, CA, USA)[5] has a pinhole mechanism. It should be remarked that the implanted lens does not have a refractive power, rather it achieves its effect by raising the center of the cornea.[6]

Small-aperture corneal inlay (SACI), commonly known as KAMRA corneal inlay, is a micro-drilled opening device with a diameter of 3.8 mm and a center hole of 1.6 mm.[7] It is made of polyvinylidene fluoride and carbon nanoparticles, and it is placed within the stroma in a corneal pocket in the non-dominant eye. It works by allowing a channel light through the small opening and blocking the unfocused light from passing through the periphery, hence increasing the depth of focus as the central opening has a pinhole effect.[7] However, as it partially blocks light, it could influence in visual performance.[8] The visual experience in the patient is different from monovision in which one eye is corrected for distance vision and the other for near vision.[9] The KAMRA inlay is opaque and has 8400 pores that allow the passage of nutrients to avoid weight loss and epithelial problems, as well as to maintain the viability of the anterior stromal lamella.[10] It is designed to allow light to pass through the pupil due to its central opening, which blocks incident light and out-of-focus light from the periphery. The inlay yields a monocular pin-hole effect but permits maintenance of binocular summation.[7]

The purpose of this study was to systematically review case series of SACI performed in emmetropic presbyopic patients in order to evaluate the visual outcomes, postoperative complications and explantation reasons.

Methods

This systematic review was carried out by searching in PubMed, Web of Science and Scopus data bases on February 12, 2020. The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations.[11] An initial search was conducted, focused on obtaining case studies of corneal inlays in presbyopic patients. The keywords used were ‘‘small-aperture corneal inlay’’ and ‘‘KAMRA inlay’’. From them, a total of 88 articles were identified, which were evaluated and selected according to inclusion and exclusion criteria. The inclusion criteria were: (1) KAMRA inlay implantation in emmetropic presbyopic patients with or without prior surgery. The exclusion criteria were: (2) narrative reviews; (3) animal studies; (4) non-English publications; (5) publications in which small-aperture corneal inlay was not performed exclusively (i.e. combined with myopic, hyperopic or astigmatism LASIK; (6) articles without findings or conclusions; (7) articles with a number of patients less or equal than 5; (8) articles in non-indexed scientific journals.

The following data was summarized in tables; (1) authors and year of publication, (2) study design, (3) maximum follow-up period expressed in months, (4) number of patients, (5) number of eyes implanted, (6) sex, (7) intrastromal flap / pocket creation technique (mechanical microkeratome or femtosecond laser), (8) pocket depth (expressed in microns, µm), (9) past medical history, namely previous surgeries, (10) visual postoperative improvements of uncorrected near visual acuity (UNVA), uncorrected intermediate visual acuity (UIVA) and uncorrected distance visual acuity (UDVA), (11) patient satisfaction rate, expressed in percentage, (12) postoperative complications after SACI (repeated cases were excluded from explantation rate), (13) explantation rate; in studies with KAMRA inlay explantation, percentage of eyes were reported in brackets, and finally, (14) explantation reason. To assess the risk of bias of the included studies, a summary table was elaborated (Table 1) based on the Quality Assessment Tool for Case Series Studies from the National Heart, Lung, and Blood Institute.[12] The questions included in the tool were: (1) Is the study oriented to a clear question?; (2) Were all the patients results taken into account?; (3) Was the follow-up complete?; Were the same conditions used in surgical treatment?; (5) Was the intervention clearly described?; (6) Was the duration of follow-up adequate?; (7) Were the results described correctly? This analysis did not result in the exclusion of any article. However, articles with a higher risk of bias had a

lower weight for the data synthesis. Risk of bias was assessed by I.PJ and JM.SG. In case of disagreements, C.RDL decided the tie-breaker.

Results

The selection process of this systematic review was presented with a flow chart diagram in Figure 1. A total of eighteen articles[9,10,13–28] published between 2011 and 2018 were included in this systematic review. All of them were case series studies. Patients completing the inclusion criteria were presbyopic between 45 and 60 years old, with a preoperative manifest spherical equivalent refraction defined as -0.75D to +0.50D, with no more than -0.75D of refractive cylinder, and uncorrected near visual acuity of 20/100 to 20/40 (Snellen scale) or 0.7 to 0.3 (Logarithm of the Minimum Angle of Resolution, LogMAR scale). Near addition target was between +1.00 diopters (D) and +2.50 D, minimum central corneal thickness (CCT) was established as 500 µm for most of the articles, a minimum central endothelial cell count (ECC) of 2000 cells/mm^2 or more, and a corneal power from 41.00 D to 47.00 D in all meridians. According to exclusion criteria, patients with anterior or posterior segment disease, any type of immunodeficiency disorder, patients using systemic medications with associated side effects, and those with latent hyperopia were not included. Patient and surgery details of the selected articles were reported in Table 2.

This systematic review included 2724 eyes from a total of 2691 patients, and a maximum postoperative follow-up that ranged from 3 to 60 months, with a mean maximum follow-up of 19 months. Fifteen articles [9,10,13–19,21,24–28] used femtosecond laser for intrastromal pocket creation, two[20,22] of them used mechanical microkeratome and one[23] did not report the surgical technique. The pocket depth ranged from 150 µm to 280 µm and the mean pocket depth was 202 µm. Results after SACI were presented in Table 3. Concerning previous ocular history of patients, there were 14 articles[9,10,14–19,21–23,25,27,28] that studied emmetropic presbyopic patients and four articles[13,20,24,26] that studied the combination with previous cataract surgery or LASIK. There were no statistically significant differences in terms of the results obtained among the patients with or without previous surgery. In the postoperative period, there was a remarkable improvement in UNVA and UIVA. In the last follow-up appointment, UNVA ranged between 44% to 100% of eyes with 20/32 or better (J2, Jaeger), with a mean UNVA of 20/32 or better in 78.50% of eyes. UIVA was reported in only five studies[15–17,23,25] and ranged between 87% to 100% of eyes with 20/32 or better. Mean UIVA was 91.80%. UDVA ranged between 65% to 100% with 20/25 or better and ranged between 65% to 100%, with a mean UDVA of 90.50% of eyes with 20/25 or better. The exact distances in which UDVA, UIVA and UNVA were measured were not reported in the included articles.

Regarding complications, keratocyte activation, corneal edema, haze, stromal thinning, iron deposits and dystrophies were reported. These issues were responsible for the explanted inlays and were the cause of the visual complaints and hyperopic changes. The number of explanted KAMRAs were 101 (3.7% from total implanted). Furthermore, 6 articles[9,10,18,19,24,25] offered information on patient satisfaction and the overall percentage was between 60% and 90%. Finally, the included studies were grouped into three levels based on the risk of bias assessment tool. The groups were: low evidence (affirmative answers = 0 to 2); medium evidence (affirmative answers = 3 to 5); and high evidence (affirmative answers = 6 to 7). No studies reported low evidence level. Moshirfar et al.,[22] Moshirfar et al.,[24] Huseynova et al.,[26] Tomita & Huseynova[13] and Waring[19] achieved a medium evidence level. Moshirfar et al.,[21] Vukich et al.,[9] Linn et al.,[23] Dexl et al.,[25] Abbouda et al.,[27] Agca et al.,[14] Tomita et al.,[28] Dexl et al.,[17] Dexl et al,[10] Seyeddain et al.,[15] Seyeddain et al.[16] Dexl et al.[18] and Yımaz et al.,[20] obtained a high evidence level.

Discussion

Visual outcomes

Postoperative results after this surgical technique proved an increase in distance visual acuity. UNVA improved in 78.5% of eyes to J2 or better. UIVA, only described in five articles,[9,15–17,25] improved in 91.80% of eyes to 20/32 or better, and UDVA was shown to improve in 90.50% of eyes to 20/25 or better. The UNVA improvement had a slight effect on the UDVA. To achieve better visual outcomes, positioning and centering must be precise. An off-center of only 0.5 mm may reduce the image quality[29,30] since the opening would not be aligned with patient's visual axis hence implying a new surgical procedure.[31] Usually, a femtosecond laser was used to create an intrastromal pocket which works using the photo disruption principle, emitting infrared pulses and achieving tissue separation at the molecular level without impacting surrounding tissue. However, there were two cases that were performed with mechanical microkeratome.[20,22] According to various authors,[32,33] femtosecond laser should be used to obtain better results in surgery. Mechanical microkeratome should be avoided due to its imprecision and its worse results.[34] However, this systematic review did not observe significant differences among both techniques.

Complications

Cases of corneal edema, blurring, stromal thinning, flap striae, epithelial growth[35] or iron deposits were some of the complications experienced by the patients included in the studies. Although the mentioned complications were localized near the Bowman's membrane, they did not influence vision and they did not influence the refractive results. In addition, they occurred less frequently in implants with reduced thickness and a greater number of pores.[36] Another frequent postoperative complication was keratocyte activation that led to corneal haze[37], therefore reducing near and intermediate visual acuity. Cases requiring explantation experienced persistent corneal haze postoperatively and preoperative visual acuity was not recovered. To avoid postoperative haze, it is proposed to use lower laser energy or to increase steroid treatment.[27] Contrast sensitivity remained within normal ranges[38] and stereopsis was compromised in some patients, mainly in poor lighting enviroments.[23] In this review, there were patients who presented topographic changes. Some of them developed hyperopic changes,[24,25] which seemed to be associated with shallower inlays. Therefore, the ideal placement of KAMRA inlay is at a depth between 250 and 350 µm.[10,17,24] The recommended residual stroma bed is established at 250 µm. It should be noted that there was no significant induction of astigmatism in any meridian.[8]

Safety

101 eyes from a total of 2692 (without repeated cases in Dexl et al.[18] and Dexl et al.[25]) required inlay explantation. The inlay implantation did not reduce corneal thickness. Consequently, it seems that it can be used in patients who have previously been laser corrected and in pseudophakic patients. Previous results suggest that there are no differences between visual outcomes of virgin eyes and eyes with previous ocular surgery.[24] Patients in this study who had previously been corrected with LASIK reported a pocket depth between 170 and 250 µm. None of the cases studied placed KAMRA inlay in the LASIK flap. No significant differences were observed between men and women. Devices can be easily removed when required. Alió et. al[39] reported that it has a minimal impact on corneal topography and aberrometry during and after recovery when extraction occurs within six months of its implantation. However, changes may be permanent if explantation is performed after this period.[7] Although a longer follow-up could be necessary, most patients, between 60% and 90%, expressed a high satisfaction rate. Moreover, the explantation rate reported was between 1.8% and 33.4%, an average of 3.7% of eyes. After explantation, most patients

recovered the near and intermediate visual acuity they had prior to implantation, but there is a risk of not being able to achieve the preoperative UDVA.[40] The long-term safety is therefore concerning and corneal inflammation requiring the inlay explantation is often not reversible resulting in significant scarring and visual impairment. Repositioning or reimplanting the corneal inlay could be an option for retreatment procedures in order to achieve the desirable refractive result once it has been removed. The main reasons for explantation were incorrect implant placement,[41,42] blurring and refractive changes.[43]

Strengths and Limitations

To the best of our knowledge, this is the first systematic review of SACI available in the scientific literature. The PRISMA method improves the evidence level available to date. Within the limitations, only eighteen studies could enroll this review, there is a lack of literature regarding randomized clinical trials comparing KAMRA with other corneal inlays, and many articles were published by the same researchers. Satisfaction rate relevance was limited since only one third of the studies provided this information. In the same way, there is a great heterogeneity in the follow-up and therefore it should be standardized. In addition, six studies [10,15–18,25] that reported the best outcomes among the included studies in this review have a risks of bias. For instance, Acufocus Inc., Irvine, California, USA, financially supported the research, authors received travel expenses from Acufocus, and other authors work as clinical specialists for Acufocus. Therefore, sixteen from eighteen studies reported conflict of interest with AcuFocus. Thus, we allow readers to weigh the results and conclusions of this systematic review. In addition, in some articles[21,22,24] [10,17,18,25] the follow-up length match with the progressively publication date. Therefore, some eyes could have been included in more than one paper making the total eye sample lower than 2724. However, it was impossible to calculate it in this study.

Small-aperture corneal inlay outcomes achieved a high efficacy and satisfaction rate, although its safety is still questionable. The inlay improves near and intermediate vision with slight effect on visual acuity at distance. Furthermore, the inlay may be explanted when necessary, although the visual acuity may not improve to the preoperative state. Surgical process, patient selection and pocket or flap depth are essential for successful surgery outcomes.

Conflicts of Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Declarations

Conflicts of interest: All authors declare no competing interest

Source of Funding: No funding support

Ethics approval: This study was conducted in accordance with the tenets of the Helsinki Declaration and obtained Institutional Review Board approval.

Consent to participate: All patients included in this work were adequately informed verbally and in writing of the benefits, characteristics, and risks of the surgeries. All patients signed an informed consent prior to the surgery and after the interview performed with the ophthalmologist.

Consent for publication: All authors consent publication of this article

Availability of data and material: Data available on demand

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Figure legends

Figure 1. Study selection process according to the PRISMA statement.

Table 1. Quality assessment of articles							
Author (date)	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**
Moshirfar et al.[21] (2018)	Yes	No	Yes	Yes	Yes	Yes	Yes
Vukich et al.[9] (2018)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Linn et al.[23] (2018)	Yes	Yes	Yes	Yes	No	Yes	Yes
Moshirfar et al.[22] (2017)	Yes	NR	Yes	No	No	Yes	Yes
Moshirfar et al.[24] (2016)	Yes	No	Yes	Yes	Yes	No	Yes
Dexl et al.[25] (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Abbouda et al.[27] (2014)	Yes	Yes	Yes	No	Yes	Yes	Yes
Agca et al. [14] (2014)	Yes	Yes	Yes	Yes	Yes	No	Yes
Huseynova et al.[26] (2014)	Yes	No	Yes	Yes	Yes	No	No
Tomita et al.[28] (2014)	Yes	Yes	Yes	Yes	Yes	No	Yes
Tomita & Huseynova[13] (2014)	Yes	NR	NR	Yes	Yes	Yes	Yes
Dexl et al.[10] (2012)	Yes	Yes	Yes	No	Yes	Yes	Yes
Dexl et al.[17] (2012)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Seyeddain et al.[15] (2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Seyeddain et al.[16] (2012)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dexl et al.[18] (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Waring IV[19] (2011)	Yes	NR	Yes	Yes	No	Yes	Yes
Yımaz et al.[20] (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes

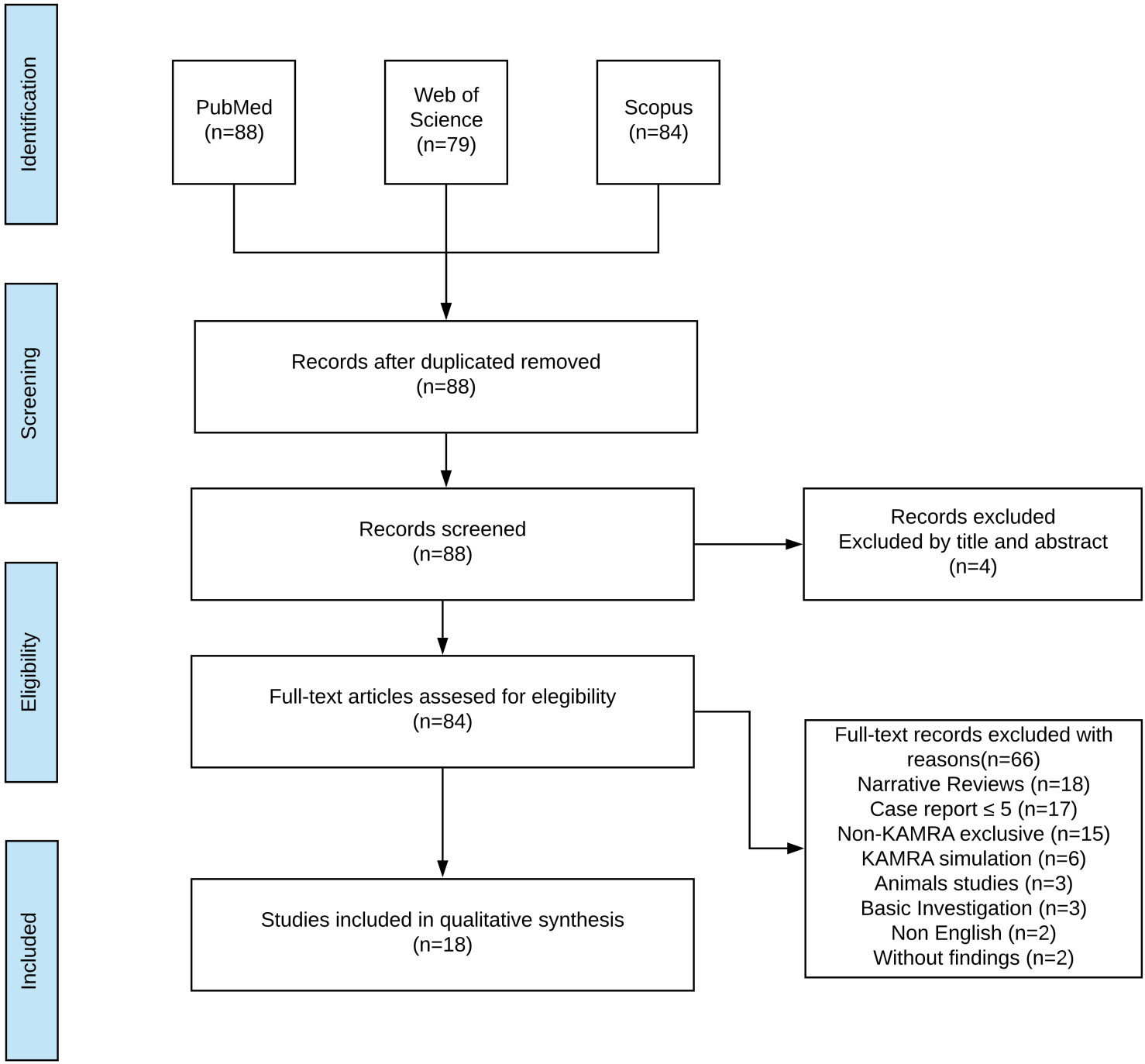
NR= Not reported; Q= Question; (Q1): Is the study oriented to a clear question?; (Q2): Were all the patients results taken into account?; (Q3): Was the follow-up complete?; (Q4): Were the same conditions used in surgical treatment?; (Q5): Was the intervention clearly described?; (Q6): Was the duration of follow-up adequate?; (Q7): Were the results described correctly?

Table 2. Study characteristics								
Autor (date)	**Design**	**AcuFocus Disclosure**	**Follow-up (months)**	**Patients**	**Eyes**	**Sex (F/M)**	**Pocket technique**	**Pocket Depth (μm)**
Moshirfar et al.[21] **(2018)**	SC	Consultant & Travel Expenses	36	50	50	13 / 37	FS	210
Vukich et al.[9] **(2018)**	SC	Consultant & Travel Expenses	36	507	507	NR	FS	185 to 270
Linn et al.[23] **(2018)**	SC	Publication Fee	6	60	60	NR	NR	NR
Moshirfar et al.[22] **(2017)**	SC	Hold Shares	24	508	508	NR	MMK	200
Moshirfar et al.[24] **(2016)**	SC	None	6	57	57	NR	FS	200 to 280
Dexl et al.[25] **(2015)**	SC	Consultant & Travel Expenses	60	32	32	7 / 25	FS	170
Abbouda et al.[27] **(2014)**	SC	None	6	12	12	NR	FS	150 to 200
Agca et al.[14] **(2014)**	SC	Consultant & Employee	6	34	68	10 / 24	FS	180 to 200
Huseynova et al.[26] **(2014)**	SC	Consultant	3	13	13	7 / 6	FS	≤ 200
Tomita et al.[28] **(2014)**	SC	Consultant	6	584	584	433 / 151	FS	200
Tomita & Huseynova[13] **(2014)**	SC	Consultant	3	151	151	NR	FS	200
Dexl et al.[10] **(2012)**	SC	Surgical Advisor, Travel Expenses & Patent Owners	24	24	24	NR	FS	200 to 270
Dexl et al.[17] **(2012)**	SC	Surgical Advisor	12	24	24	NR	FS	230
Seyeddain et al.[15] **(2013)**	SC	Surgical Advisor & Travel Expenses	24	24	24	NR	FS	NR
Seyeddain et al.[16] **(2012)**	SC	Surgical Advisor & Travel Expenses	36	32	32	NR	FS	170
Dexl et al.[18] **(2011)**	SC	Surgical Advisor	24	32	32	NR	FS	NR
Waring IV[19] **(2011)**	SC	Financial Interest	18	508	507	NR	FS	NR
Yımaz et al.[20] **(2011)**	SC	Consultant	12	39	39	17 / 22	MMK	170

F/M= Female / Male; SC= Serie of Cases; FS= Femtosecond laser; NR= Not reported; MK= mechanical microkeratome

Table 3. Evaluation of the visual results after the implantation of Small-Aperture Intracorneal Inlay								
Autor (date)	**Previous history**	**UNVA***	**UIVA***	**UDVA***	**Satisfaction** (%)**	**Postoperative complications**	**Explantation Yes/No (%)**	**Explantation Reason**
Moshirfar et al.[21] (2018)	EP	86%	-	88%	NR	KA	Yes (8%)	NR
Vukich et al.[9] (2018)	EP	72%	87%*	92%	90 (3 to 36)	CE, BDV and ST	Yes (8.7%)	CC
Linn et al.[23] (2018)	EP	85%	-	100%	NR	↓Stereopsis 25%	No	-
Moshirfar et al.[22] (2017)	EP	70%		-	NR	↓VA, ↑ IOP, DLK	Yes (8.5%)	BDV
Moshirfar et. al[24] (2016)	64% EP, 22% PLP and 4% PPP	44%	-	65%	60 (3 & 6)	None	Yes (1.8%)	HS
Dexl et al.[25] (2015)	EP	74%	87%*	94%	83.9 (60)	PIP, FS and ID	Yes (3.1%)	HS
Abbouda et al.[27] (2014)	EP	-	-	-	NR	KA and BDV	Yes (33.4%)	PIP and BDV
Agca et al.[14] (2014)	EP	-	-	-	NR	None	No	-
Huseynova et al.[26] (2014)	PPP	46%	-	85%	NR	NR	No	-
Tomita et al.[28] (2014)	EP	-	-	-	NR	None	No	-
Tomita & Huseynova[13] (2014)	PLP	80%	-	90%	NR	Infections and ED	No	-
Dexl et al.[10] (2012)	EP	-	-	-	NR	EG, ID and BDV.	No	-
Dexl et al.[17] (2012)	EP	95%	90%*	100%	75 (3 to 24)	KA	No	-
Seyeddain et al.[15] (2013)	EP	100%	100%*	95%	NR	None	No	-
Seyeddain et al.[16] (2012)	EP	95%	95%*	90%	NR	None	No	-
Dexl et al.[18] (2011)	EP	-	-	-	84.5 (3 to 12)	ID	No	-
Waring IV[19] (2011)	EP	-	-	-	75 (NR)	None	No	-
Yımaz et al.[20] (2011)	EP and PLP	96%	-	96%	NR	None	Yes (10.3%)	Cataracts

EP: emmetropic presbyopia; PLP: post-LASIK presbyopia; PPP: *pseudo-phakic presbyopia; UNVA: uncorrected near visual acuity; UIVA:* uncorrected *intermediate visual acuity; VA: visual acuity; IOP: Intraocular pressure; DLK: diffuse lamellar keratitis; BV: binocular vision; NR: not reported; KA: keratocyte activation; CE: corneal edema; BDV: blur distance vision; ST: stromal thinning; PIP: poor implant placement; FS: flap striae; ED: endothelial degeneration; EG: epithelial growth; ID: iron deposits; CC: corneal cyst; HS: hyperopic shift; * Percentage of eyes with 20/32 or better **Percentage of eyes with 20/25 or better.**Include in brackets the satisfaction time collected (expressed in months)*


Identification
Screening
Eligibility
Included
PubMed (n=88)
Web of Science (n=79)
Scopus (n=84)
Records after duplicated removed (n=88)
Records screened (n=88)
Records excluded
Excluded by title and abstract (n=4)
Full-text articles assesed for elegibility (n=84)
Full-text records excluded with reasons(n=66)
Narrative Reviews (n=18)
Case report ≤ 5 (n=17)
Non-KAMRA exclusive (n=15)
KAMRA simulation (n=6)
Animals studies (n=3)
Basic Investigation (n=3)
Non English (n=2)
Without findings (n=2)
Studies included in qualitative synthesis (n=18)