

Combined corneal wavefront-guided transepithelial photorefractive keratectomy and accelerated corneal collagen cross-linking following intracorneal ring segment implantation in management of moderate keratoconus

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Access this article online
Quick Response Code:

Website: www.saudijophthalmol.org
DOI: 10.4103/sjopt.sjopt_26_20

Abstract:

PURPOSE: Keratoconus (KC) leads to gradual progressive loss of vision in young and adult patients. For the purpose of visual rehabilitation and for hindering KC progression in patients, we designed this study. The main aim of this study is to help the KC patients to improve and stabilize their vision.

METHODS: This prospective consecutive uncontrolled study includes 36 eyes of 36 patients with moderate degree of KC. All patients underwent combined wavefront-guided transepithelial photorefractive keratectomy (TPRK) and accelerated corneal collagen cross-linking (ACXL) after intracorneal ring segment (ICRS) implantation. Different measures will be evaluated at baseline, after ICRS implantation, and at one, 3, 6, and 12 months after combined (TPRK and ACXL). These measurements are uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refraction spherical equivalent (MRSE), corneal indices based on Scheimpflug tomography, and higher-order aberrations (HOAs) based on (Sirius, Schwind) tomography.

RESULTS: There were significant improvements in logMAR (UDVA and CDVA) and reduction in sphere, manifest cylinder, MRSE, maximal keratometry, and mean keratometry after ICRS implantation in the first stage. After TPRK and ACXL as the second stage, there were significant improvements in visual acuity of both logMAR UDVA and CDVA. Reduction in refractive outcomes, including MRSE, sphere, and manifest cylinder. All corneal indices including steep, flat, mean, and maximal keratometries had been decreased. Furthermore, there were significant improvements in the final root mean square, HOAs, and coma aberrations from baseline.

CONCLUSION: In moderate KC, triple therapy of ICRS implantation followed by combined TPRK and ACXL appears to be a safe and effective approach. This approach provides an improvement in visual acuity, refraction, corneal indices, and HOAs. These improvements were maintained for 1 year postoperatively. It also halts KC progression.

Keywords:

Corneal collagen cross-linking, corrected distance visual acuity, higher-order aberrations, intracorneal ring segment implantation, keratoconus, transepithelial photorefractive keratectomy, uncorrected distance visual acuity

INTRODUCTION

Keratoconus (KC) is a progressive, noninflammatory, asymmetric, and usually bilateral ectatic disease of the cornea. Disease onset usually begins at puberty, and it is

characterized by localized corneal thinning, visual distortion, corneal steepening, and central corneal scarring. In patients with KC, visual rehabilitation has been achieved through different approach combinations of

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How to cite this article: Bakhsh AM, Elwan SA, El-Atris TM, Al-Salowie AM, Alsamnan MS. Combined corneal wavefront-guided transepithelial photorefractive keratectomy and accelerated corneal collagen cross-linking following intracorneal ring segment implantation in management of moderate keratoconus. Saudi J Ophthalmol 2022;36:53-63.

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Submitted: 13-Oct-2020

Revised: 20-Feb-2022

Accepted: 07-Mar-2022

Published: 11-Jul-2022

intracorneal ring segment (ICRS) implantations, CXL, and photorefractive keratectomy (PRK) or deep anterior lamellar keratoplasty (DALK). ICRS implantations have been used for the refractive rehabilitation of KC by flattening the corneal center.^[1] ICRS reduces refractive error, stabilizes the corneal shape, and increases tolerance to contact lens users. It has been shown that ICRS can reduce corneal astigmatism, the mean keratometry values, and coma aberrations.^[2-4] However, the refractive outcomes of ICRS alone are unpredictable, and the procedure does not control the progression of KC.^[5,6] On the other hand, corneal collagen cross-linking (CXL) can be used to induce the development of strong chemical bonds between the collagen fibers of the corneal stroma. CXL alone can halt disease progression, yet it can minimally reduce the refractive error and corneal steepening.^[7,8] Topography-guided photorefractive keratectomy has the advantage of improving myopia and astigmatism; nonetheless, such an exclusive approach may lead to corneal thinning and KC progression.^[9,10] Therefore, different combinations of ICRS implantations, CXL, and transepithelial photorefractive keratectomy (TPRK) seem to provide plausible approaches to achieve better visual outcomes. Previous studies have reported additional benefits of combined ICRS implantation and CXL on the visual improvement and keratometry indices.^[11,12] In addition, combined CXL and PRK have also been studied for the KC management.^[13-16] In patients with moderate KC, a same-day combination of TPRK and CXL after ICRS implantation has led to significant improvements in the uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), and keratometry indices with or without improvements in coma aberrations postoperatively.^[17,18] For the progressive cases, a three-step procedure comprising ICRS implantation, TPRK, and CXL has resulted in improvements in logMAR (UDVA and CDVA), manifest refraction spherical equivalent (MRSE), and reduction in the mean keratometry values for the steep and flat meridians.^[19] Both accelerated and standard CXL in combination with the same-day TPRK and single inferior ICRS were effective for both visual and topographical outcomes.^[20,21]

Based on such encouraging results, we hypothesized that triple approach of corneal wavefront-guided TPRK and accelerated corneal CXL (ACXL) following ICRS implantation might also induce visual functional improvements in moderate KC patients. Therefore, the objective of our study is to assess the efficacy and safety of ICRS implantation followed by a combined corneal wavefront-guided TPRK and ACXL in patients with moderate progressive KC.

METHODS

A prospective, uncontrolled case series was conducted involving consecutive patients diagnosed with moderate KC. They underwent combined corneal wavefront-guided TPRK and accelerated corneal CXL at least 3 months after ICRS implantation. The study was carried out during the period between October 2018 and April 2020 at the Security Forces

Hospital (SFHP), Ophthalmology Department, Riyadh, Saudi Arabia. An ethical approval was obtained from the SFHP Ethical Board Committee (Institutional Review Board Registration Number: 18-289-54), and the study procedures were in accordance with the principles of the Declaration of Helsinki Tents and the Good Clinical Practice guidelines. The study protocol was registered in the ClinicalTrials.gov registry (identifier: NCT04383301). All patients provided informed written consent for the conduct of the study and for publication.

Eligibility criteria

Adult patients (> 25 years) who had been intolerant to contact lens use were eligible. They should have been diagnosed with moderate keratoconus (45-54 D in both meridians) without corneal scarring and/or central pachymetry $\geq 400 \mu\text{m}$, and if disease progression had been noted over the past 6 months. All included patients had undergone this triple procedure of combined corneal wavefront-guided TPRK and corneal ACXL at least 3 months after ICRS implantation. Patients with central or paracentral corneal scarring, central pachymetry $< 400 \mu\text{m}$, and a systemic autoimmune disease, as well as those with a history of herpetic keratitis, pregnancy, lactation, or severe dry eye syndrome, were excluded. Grading of KC was based on the Amsler-Krumeich classification.^[22,23] Progression was defined as one or more of the following changes over a period of 6 months: an increase of ≥ 1.00 diopter (D) in maximal keratometry values, an increase of ≥ 1.00 D in manifest cylinder, an increase of ≥ 0.50 D in MRSE, and a reduction of $> 12 \mu\text{m}$ in the thinnest pachymetry.

Examinations and measurements

At baseline, the preoperative examination included UDVA, CDVA, manifest and cycloplegic refraction, slit-lamp biomicroscopy, tonometry, Pentacam camera, tomography, and dilated fundus examination using binocular ophthalmoscopy. Patients should have stopped using contact lenses 3 weeks before the date of clinical examination. A complete medical history, including any systemic diseases, was recorded. All patients underwent a complete ophthalmic examination (UDVA and CDVA with a Snellen chart and manifest refraction) after ICRS implantation and before combined TPRK and ACXL (first stage), and at 1, 3, 6, and 12 months after combined TPRK and ACXL (second stage). Corneal indices were measured at the 8-mm zone using the Scheimpflug tomography system with Pentacam camera (OCULUS-Netzteil Art, Pentacam HR, Germany). These included the flat (K1) and the steep meridian (K2), as well as the mean central keratometry (mean K) and maximum simulated keratometry (Kmax). Corneal topographic data were obtained from the Sirius topography (Sirius, SCHWIND eye-tech-solutions GmbH, Kleinostheim, Germany) to measure changes in corneal aberrations, including higher-order aberrations (HOAs), coma, and spherical aberrations. Root mean square (RMS) values of the corneal HOAs were fitted with a 7th order Zernike expansion and were used for subsequent analysis. Wound healing time and the onset of any

postoperative complications were reported. Patients were asked to report their satisfaction levels regarding the procedure, and they were advised to adhere to follow-up visits.

The surgical technique

First-stage procedure

Before the surgery, tetracaine hydrochloride 0.5% ophthalmic solution (Bausch and Lomb, Minims) and moxifloxacin 0.5% (Vigamox, Alcon Co.) drops were instilled three times within a 5-min interval. The eyelids were prepared with antiseptic chlorhexidine gluconate 0.05% solution (Saudi Medical Solution Company). All patients underwent femtosecond laser which enabled ICRS implantation. An Intacs SK intracorneal ring (6.0-mm optical zone; fixed arc length of 150°; angulation 30°) was implanted in the cornea. The ring segment thickness sizes were decided according to the nomogram provided by the manufacturer.^[24] The incision was placed at the steepest meridian, and the depth of the ring tunnel was set at 75%–80% of the thinnest pachymetry reading. After surgery, a bandage contact lens (BIOMEDICS Evolution CL Ocufilecon D 45% and water 55%) was placed to be removed after incision healing. In addition, the following ophthalmic medications were applied on the treated eye: moxifloxacin 0.5% (Vigamox, Alcon Co.) eye drops QID for 2 weeks, Tobradex eye drops (tobramycin 0.3%-dexamethasone 0.1%, Alcon Co.) QID with tapering dose for 1 month, and sodium hyaluronate 0.2% (Hyfresh, Jamjoom Pharma Co.) eye drops QID for 3 months.

Second-stage procedure

After at least 3 months from the ICRS implantation, patients were conditionally selected if they have had stabilized keratometry values (not reduced by >1 D from the previous visit). Eligible patients were then scheduled for a combined approach of corneal wavefront-guided TPRK and ACXL. TPRK between the corneal ring segments was performed using Amaris excimer LASER 193 nm, version 750 S (Schwind eye-tech-solutions GmbH and Co. KG, Mainparkstrasse, Kleinostheim, Germany). The integrated Optimized Refractive Keratectomy-Custom Ablation Manager software was used to plan the ablation profile (Schwind eye-tech-solutions GmbH and Co. KG). This was based on clinical parameters, including pachymetry, corneal wavefront data, and manifest refraction, as well as topography data from the Sirius topographer. The maximum ablation depth was limited to (50–60 μm). Mitomycin C 0.02% was then applied for 20 s to reduce postoperative haze, and this was followed by eye irrigation with a balanced saline solution (BSS). After the excimer laser corneal ablation, the corneal surface was immediately soaked with riboflavin 0.1% and hydroxypropyl methylcellulose (Vibex Rapid; Avedro Inc., Waltham, MA, USA). A riboflavin solution was added at 2-min intervals during the soaking process, after which the eye was irrigated with cold BSS. After the completion of soaking, UVA exposure (wavelength: 365 nm) was performed for 10 min at an irradiance of 9 mW/cm², to give a total radiant exposure of 5.4 J/cm², with the application of intermittent riboflavin

drops during the exposure. At the end of the surgery, a bandage contact lens was placed, and the same previous postoperative medications were used. A pain relief oral medication was prescribed as needed.

Statistical analysis

Patients' data were recorded in a Microsoft Excel Sheet and then exported to the GraphPad Prism software (version 8). Data were tested for normality using Anderson–Darling test prior to any statistical analysis, and the data were normally distributed. Continuous data were expressed as means \pm standard deviation (SD). Paired Student's *t*-test was used to compare the logMAR mean values of UDVA, CDVA, and the mean values of MRSE. One-way ANOVA was used to analyze the differences in corneal indices at different follow-up time points. To assess the efficacy and safety of the performed procedures, the efficacy index was calculated using the following formula: mean postoperative UDVA at 1, 3, 6, and 12 months/mean preoperative CDVA, whereas the safety index was computed using the formula: mean postoperative CDVA at 1, 3, 6, and 12 months/mean preoperative CDVA. The mean postoperative ratios were compared to preoperative ratios using a one-way ANOVA test. For all tests, $P < 0.05$ was considered statistically significant.

RESULTS

The study included 36 eyes of 36 patients (20 males and 16 females). Table 1 demonstrates the baseline demographic characteristics of patients. The mean age of patients was 31.56 ± 3.31 years (range: 26–37 years). KC was diagnosed in the right eye in 24 patients. The mean \pm SD refractive errors were -2.11 ± 2.89 D (sphere), -4.083 ± 1.15 D (cylinder), and -3.88 ± 3.29 D (MRSE). The mean values of logMAR UDVA and logMAR CDVA were 0.92 ± 0.31 and 0.32 ± 0.20 , respectively. Regarding corneal indices, the mean value of K1 was 46.34 ± 2.98 , K2 was 50.31 ± 2.33 , mean K was 48.19 ± 2.70 , and maximal keratometry value (Kmax) was 57.68 ± 6.58 . ICRS was performed after an average of 3.9 ± 2.2 months (range: 3–5 months) from baseline. All surgical procedures were successfully performed, and no major postoperative complications were reported during the follow-up period. Table 2 demonstrates the results of the comparative analyses of pre- and post-ICRS indicators of visual acuity, refractive outcomes, and corneal indices.

The reported outcomes after intracorneal ring segment

As shown in Table 2, after at least 3 months of ICRS implantation (this stage will be termed “before TPRK + ACXL” in the following sections), there were significant improvements in the mean logMAR UDVA ($P < 0.0001$) and logMAR CDVA ($P = 0.002$), as well as significant reductions in the refractive outcomes, including the mean sphere ($P = 0.011$), the mean cylinder ($P < 0.0001$), and the mean MRSE ($P < 0.0001$) as compared to baseline values. Moreover, as demonstrated in Table 3, mean corneal indices improved significantly, including the flat meridian (K1, $P < 0.0001$), the steep meridian (K2,

Table 1: Patients' demographic data

Item	Description
Age, years (mean±SD), average	31.56±3.31 (26–37)
Sex (male/female)	20/16
Laterality (R/L)	24/12
Refractive errors (D) (mean±SD)	
Sphere	-2.11±2.89 (-7-1.5)
Cylinder	-4.083±1.15 (-5.5--2)
MRSE	-3.88±3.29 (-9.5-1.5)
Visual acuity (logMAR) (mean±SD), average	
UDVA	0.92±0.31 (0.50-1.3)
CDVA	0.32±0.20 (0-0.7)
Corneal indices (mean±SD), average	
K1	46.34±2.98 (42.4-52.4)
K2	50.31±2.33 (47.4-54.2)
Mean K	48.19±2.70 (45.5-52.9)
Kmax	57.68±6.58 (47.9-71.2)
Operative parameters (mean±SD), average	
CCT (μm)	440.7±21.52 (410-473)
Optical zone (mm)	6.72±0.23 (6.3-7.7)
Transitional zone (mm)	0.95±0.31 (0.46-1.52)
Ablation depth (μ)	33.64±11.31 (12-53)
Ablation time (s)	29.14±8.68 (10-57)

CCT: Central corneal thickness, CDVA: Corrected distance visual acuity, K1: Flat keratometry values, K2: Steep keratometry values, Kmax: Maximum simulated keratometry, L: Left eye, Mean K: Mean central keratometry, MRSE: Manifest refraction spherical equivalent, R: Right eye, UDVA: Uncorrected distance visual acuity, SD: Standard deviation

$P < 0.0001$), the mean K ($P < 0.0001$), and Kmax ($P = 0.017$). There were also significant reductions in RMS HOAs and coma aberrations ($P < 0.0001$ for both).

The reported outcomes after transepithelial photorefractive keratectomy and accelerated corneal collagen cross-linking

Visual acuity outcomes

Table 2 and Figure 1 show the main visual acuity outcomes. There were significant improvements in the mean logMAR UDVA and logMAR CDVA at 3, 6, and 12 months than baseline values ($P < 0.0001$, for all). In addition, both parameters significantly improved at the last follow-up visit (12 months after the combined approach) as compared to before TPRK + ACXL ($P = 0.002$ for logMAR UDVA and $P = 0.007$ for logMAR CDVA). However, visual acuity parameters did not change significantly at 6 or 12 months after TPRK + ACXL compared to those at 3 months after the combined approach, indicating that these parameters have stabilized at 6 months onward.

Refractive outcomes

Compared to baseline, the mean values of all refractive parameters, including sphere, cylinder, and MRSE, were significantly reduced in all time intervals after TPRK + ACXL ($P < 0.0001$ for all). Compared to the refractive values reported during patients' visits before TPRK + ACXL, only sphere and MRSE decreased at 3 months ($P = 0.004$ and 0.032 , respectively), yet all parameters decreased at 12 months

after TPRK + ACXL ($P = 0.007$ for sphere, $P = 0.001$ for cylinder, and $P = 0.038$ for MRSE). Similar to the visual acuity outcomes, there were no significant changes in the refractive parameters at 6 and 12 months in relation to the first visit after TPRK + ACXL, indicating their stabilization [Table 2 and Figure 1].

Corneal index outcomes

Table 3 and Figure 2 show the outcomes of corneal indices, RMS HOAs, and coma aberrations reported before and after TPRK + ACXL. Results revealed statistically significant improvements in all corneal indices reported in all visits after TPRK + ACXL compared to baseline parameters ($P < 0.0001$ for all). Likewise, considering corneal indices before the combined surgeries as a reference, the improvements in all parameters were significant at 3 months ($P = 0.001$, $P = 0.015$, $P = 0.003$, and $P = 0.007$ for K1, K2, mean K, and Kmax, respectively) and at 12 months after TPRK + ACXL ($P = 0.0001$, $P = 0.0005$, $P = 0.00001$, and $P = 0.001$ for K1, K2, mean K, and Kmax, respectively). The mean values of corneal indices have not changed at 6 and 12 months compared to those revealed at 3 months postoperatively.

Higher-order aberration outcomes

The RMS of HOAs decreased significantly in a consistent manner after TPRK + ACXL compared to preoperative values ($P < 0.0001$ for all), and the changes were also significant at 6 ($P = 0.012$) and 12 months ($P = 0.001$) compared to those reported at 3 months after undergoing TPRK + ACXL. Regarding coma aberrations, there were statistically significant differences in the mean postoperative values at all time intervals compared to before surgeries ($P < 0.0001$ for all); however, no significant changes were reported at 6 and 12 months compared to 3 months after surgeries [Table 3 and Figure 2].

The efficacy and safety indices

As demonstrated in Table 4, the efficacy index of the procedures in which it was $0.72 \pm$ at post ICRS (first stage) and increased gradually and consistently with time to 0.9 at 1 month post TPRK + ACXL (second stage) and to 1.18 at 12 months post TPRK + ACXL with statistically significant difference ($P = 0.03$ and $P = 0.001$), respectively. For the safety index, it was greater than one at all time points with statistically significant difference only in comparing post ICRS (first stage) and at 12 months post (TPRK and ACXL), in which it was 1.18 versus 1.67, respectively ($P = 0.001$). There is no eye lost single line from the preoperative CDVA. Mild degree of nonsignificant corneal haze was observed at early follow-up visits in 75% of patients and disappeared completely at 6 and 12 months after TPRK and ACXL. There were no other serious complications such as ICRS protrusion or migration, persistent corneal epithelial defect, or severe keratitis.

On the last follow-up patient's questionnaire, most of the patients, 33 out of 36 (88.9%), reported that they were satisfied with the procedure outcomes and 4 patients (11.1%) reported no satisfaction. -Three of the unsatisfied patients were suffering from postoperative dryness and night glare and one

Table 2: Visual acuity and refractive changes over time

	Preoperative baseline	Before TPRK + ACXL 1 st stage	P ^a	3 months after TPRK + ACXL 2 nd stage	P ^b	6 months after TPRK + ACXL	P ^c	12 months after TPRK + ACXL	P ^d	P ^e	P ^f	P ^g	P ^h
LogMAR UDVA	0.92±0.31 (0.50-1.3)	0.39±0.23 (0.1-0.7)	<0.0001	0.30±0.21 (0.0-0.7)	<0.0001	0.22±0.20 (0.0-0.5)	<0.0001	0.19±0.17 (0.0-0.5)	<0.0001	0.54	0.002	0.68	0.29
LogMAR CDVA	0.32±0.20 (0.0-0.7)	0.19±0.14 (0.0-0.5)	0.002	0.14±0.18 (0.0-1)	<0.0001	0.09±0.1 (0.0-0.3)	<0.0001	0.04±0.06 (0.0-0.2)	<0.0001	0.65	0.007	0.75	0.09
Sphere (D)	-2.11±2.89 (-7.1-1.5)	-0.77±1.96 (-5.1-1.25)	0.011	-0.69±1.11 (-1-2.50)	<0.0001	0.64±0.85 (-0.5-2.25)	<0.0001	0.61±0.93 (-0.75-2.50)	<0.0001	0.004	0.007	>0.99	0.99
Cylinder (D)	-4.083±1.15 (-5.5--2)	-1.94±0.91 (-3.5--0.5)	<0.0001	-1.63±0.67 (-2.75--0.5)	<0.0001	-1.37±0.51 (-2.5--0.5)	<0.0001	1.16±0.80 (-2.5--1.75)	<0.0001	0.53	0.001	0.67	0.12
MRSE (D)	-3.88±3.29 (-9.5--1.5)	-1.33±2.50 (-6-1.5)	<0.0001	-0.03±0.96 (-1.75-1)	<0.0001	-0.055±0.91 (-2-1)	<0.0001	-0.055±0.81 (-2-0.75)	<0.0001	0.032	0.038	>0.99	>0.99

P^a: P value for the difference between baseline and before TPRK + ACXL (after ICRS), P^b: P value for the difference between baseline and 3 months after TPRK + ACXL, P^c: P value for the difference between baseline and 6 months after TPRK + ACXL, P^d: P value for the difference between baseline and 12 months after TPRK + ACXL, P^e: P value for the difference between before TPRK + ACXL and 3 months after TPRK + ACXL, P^f: P value for the difference between before TPRK + ACXL and 6 months after TPRK + ACXL, P^g: P value for the difference between before TPRK + ACXL and 12 months after TPRK + ACXL, P^h: P value for the difference between before TPRK + ACXL and 12 months after TPRK + ACXL. ACXL: Accelerated collagen cross-linking, CDVA: Corrected distance visual acuity, TPRK: Transepithelial photorefractive keratectomy, UDVA: Uncorrected distance visual acuity, MRSE: Manifest refraction spherical equivalent, ICRS: intracorneal ring segment, LogMAR: Logarithm of the Minimum Angle of Resolution

Table 3: Corneal index root mean square higher-order and coma aberrations

	Preoperative baseline	Before TPRK + ACXL 1 st stage	P ^a	3 months after TPRK + ACXL 2 nd stage	P ^b	6 months after TPRK + ACXL	P ^c	12 months after TPRK + ACXL	P ^d	P ^e	P ^f	P ^g	P ^h
K1 (D)	46.34±2.98 (42.4-52.4)	43.88±2.09 (41.6-48.9)	<0.0001	42.02±1.45 (39.6-44.6)	<0.0001	41.69±1.48 (39.6-44.5)	<0.0001	41.67±1.52 (39.6-44.5)	<0.0001	0.001	0.0001	0.95	0.94
K2 (D)	50.31±2.33 (47.4-54.2)	46.6±1.97 (44.1-50.9)	<0.0001	45.1±1.97 (42.5-47.7)	<0.0001	44.72±1.81 (42.5-47.3)	<0.0001	44.62±1.93 (42-47.5)	<0.0001	0.015	0.0005	0.93	0.85
Mean K (D)	48.19±2.70 (45.5-52.9)	45.19±1.94 (43.5-49.9)	<0.0001	43.5±1.73 (40.5-45.8)	<0.0001	43.06±1.67 (40.7-45.5)	<0.0001	43.09±1.68 (41-45.5)	<0.0001	0.003	0.0001	0.87	0.90
Kmax (D)	57.68±6.58 (47.9-71.2)	54.06±5.85 (47.6-67.4)	0.017	50.11±3.79 (46.5-56.8)	<0.0001	49.56±3.78 (46-56.5)	<0.0001	49.53±3.75 (46-56.3)	<0.0001	0.007	0.001	0.98	0.98
RMS, HOAs (µm)	3.89±1.24 (2.45-6.2)	2.88±0.54 (2.16-3.62)	<0.0001	1.36±0.29 (1.16-2.14)	<0.0001	0.87±0.19 (0.62-1.08)	<0.0001	0.76±0.25 (0.45-1.02)	<0.0001	<0.0001	<0.0001	0.012	0.001
Coma aberration (µm)	2.25±0.52 (1.64-2.98)	1.53±0.40 (1.14-2.28)	<0.0001	0.85±0.21 (0.62-1.28)	<0.0001	0.67±0.25 (0.42-1.18)	<0.0001	0.62±0.30 (0.36-1.28)	<0.0001	<0.0001	<0.0001	0.21	0.06

P^a: P value for the difference between baseline and before TPRK + ACXL (after ICRS), P^b: P value for the difference between baseline and 3 months after TPRK + ACXL, P^c: P value for the difference between baseline and 6 months after TPRK + ACXL, P^d: P value for the difference between before TPRK + ACXL and 3 months after TPRK + ACXL, P^e: P value for the difference between before TPRK + ACXL and 6 months after TPRK + ACXL, and P^f: P value for the difference between before TPRK + ACXL and 12 months after TPRK + ACXL, P^g: P value for the difference between before TPRK + ACXL and 12 months after TPRK + ACXL, P^h: P value for the difference between before TPRK + ACXL and 12 months after TPRK + ACXL. ICRS: intracorneal ring segment, ACXL: Accelerated collagen cross-linking, K1: Flat keratometry values, K2: Steep keratometry values, Kmax: Maximum simulated keratometry, Mean K: Mean central keratometry, RMS HOAs: Root mean square of higher-order aberrations, TPRK: Transepithelial photorefractive keratectomy

Table 4: Efficacy and safety indices

	Before TPRK + ACXL (1 st stage)	1 month after TPRK + ACXL (2 nd stage)	3 months after TPRK + ACXL	6 months after TPRK + ACXL	12 months after TPRK + ACXL	<i>P</i> ^a	<i>P</i> ^b	<i>P</i> ^c	<i>P</i> ^d
Efficacy index	0.72±0.08	0.90±0.12	0.90±0.13	1.09±0.16	1.18±0.2	0.03	0.001	1	0.07
Safety index	1.18±0.09	1.27±0.14	1.38±0.15	1.56±0.2	1.67±0.25	0.1	0.001	0.09	0.06

P^a: *P* value for the difference between before TPRK + ACXL and 1 month after TPRK + ACXL, *P*^b: *P* value for the difference between before TPRK + ACXL and 12 months after TPRK + ACXL, *P*^c: *P* value for the difference between 3 months and 12 months after TPRK + ACXL, and *P*^d: *P* value for the difference between 6 months and 12 months after TPRK + ACXL. Efficacy index: The mean postoperative UDVA/the mean preoperative CDVA, Safety index: The mean postoperative CDVA/the mean preoperative CDVA. ACXL: Accelerated collagen cross-linking, TPRK: Transepithelial photorefractive keratectomy, CDVA: Corrected distance visual acuity, UDVA: Uncorrected distance visual acuity

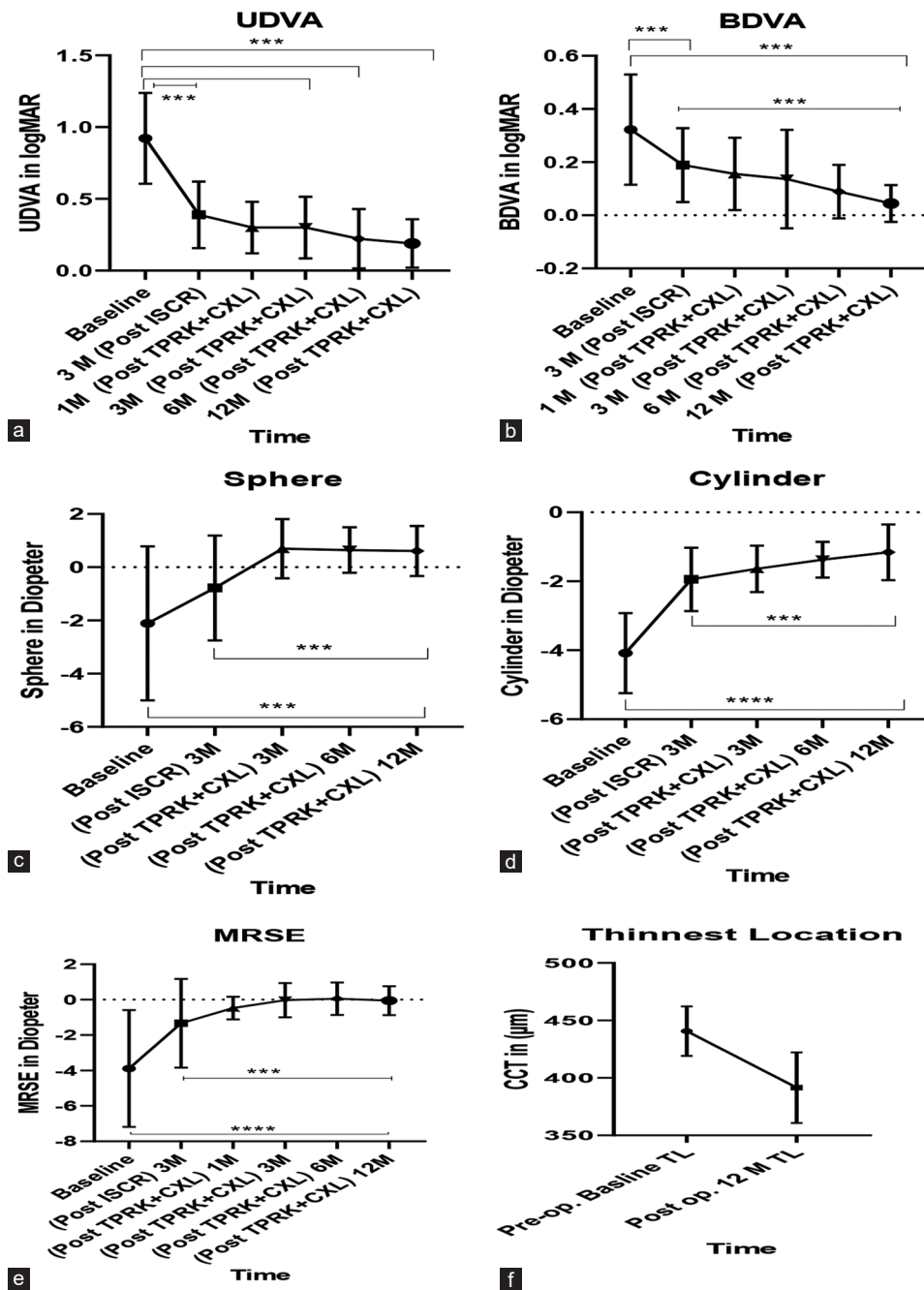


Figure 1: Changes in the parameters of visual acuity (a and b), refractive errors (c-e), and thinnest central corneal location (f)

developed postoperative mild bacterial keratitis one week after the second stage (TPRK and ACXL) who was admitted to the

hospital for 48 hours and a corneal scrape sample collected for microbiological analysis and revealed (staphylococcus aureus).

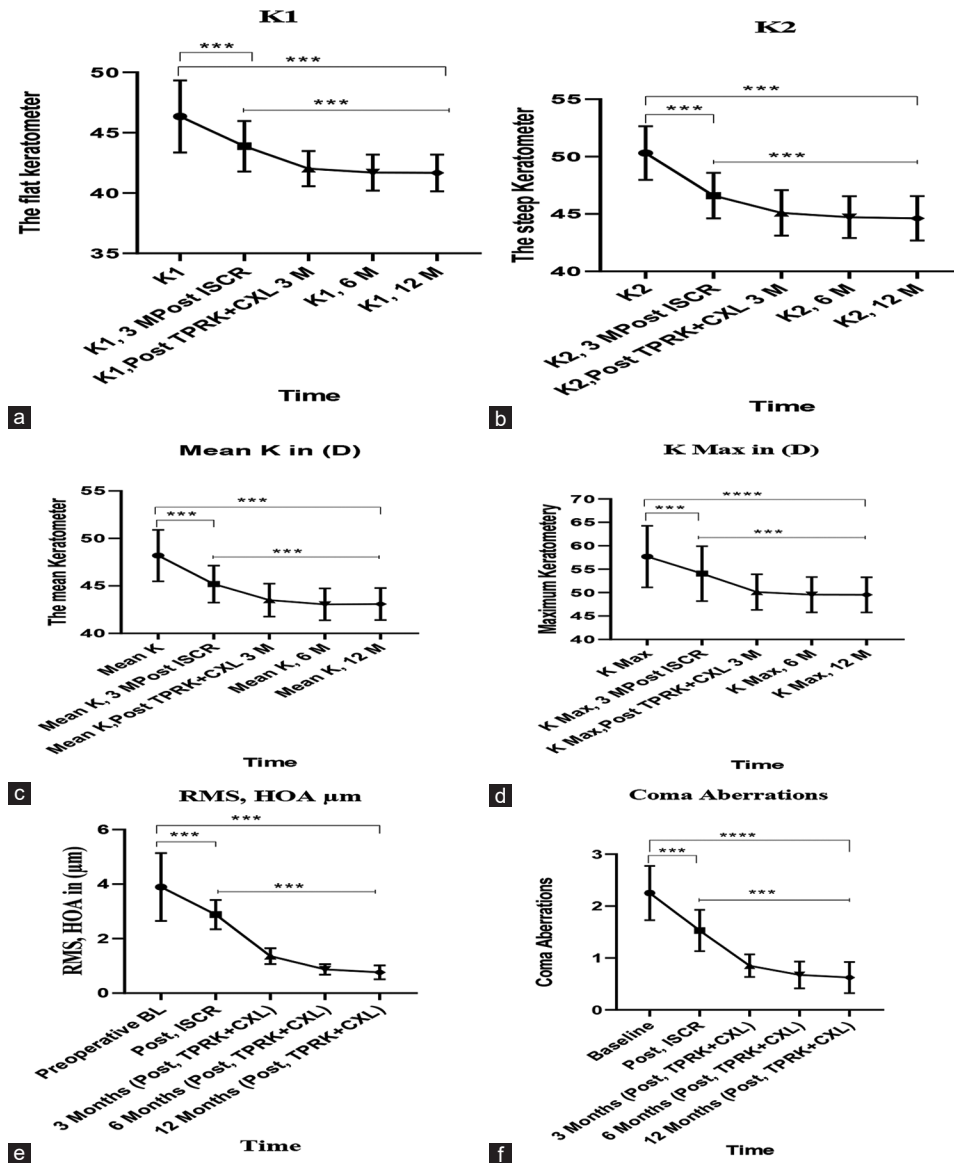


Figure 2: Changes in the corneal indices (a-d), root mean square of higher-order aberrations (e), and coma aberrations (f)

The patient well managed with fortified antibiotics eye drops 1 drop of cefazolin (50 mg/mL) every hour alternating with 1 drop of vancomycin (50mg/mL) every hour. The patient eye was improved with final log- MAR (CDVA) 0.3 equal to the preoperative one.

DISCUSSION

Combined surgical approaches for KC management have increasingly attracted the attention of ophthalmologists. With the recent advances in the interventional armamentarium, it is possible to obtain promising efficacy and safety outcomes after KC surgeries. The results of the present prospective case series showed significant improvements in the visual acuity outcomes and refractive and corneal indices among patients with moderate KC who underwent ICRS followed by TPRK + ACXL. Such improvements were apparent at

3 months after the combined TPRK + ACXL approach, and all parameters have stabilized thereafter (up to 12 months). The aforementioned outcomes emphasize the importance of each intervention for visual rehabilitation. Significant differences were noted in all parameters under investigation early after performing ICRS. The latter comprises implanting polymethyl methacrylate pieces in the mid-peripheral deep corneal stroma to reduce the central corneal curvature. In the present study, we used Intacs® SK Corneal Implants (Addition Technology, Inc. Sunnyvale, CA, USA). Based on the results of Ganesh *et al.*,^[25] the benefits of ICRS in KC patients include visual acuity improvement, reduction of irregular astigmatism, and corneal flattening. While other reports have indicated significant improvements in CDVA, UDVA, and refractive error after ICRS.^[5,26] Others found no statistically significant changes in corneal HAOs after the procedure.^[27] Indeed, the procedure did not control disease progression. Accordingly,

ACXL may be useful as a subsequent adjunct procedure. Wollensak *et al.*^[28] demonstrated that CXL stabilizes stromal collagen and hardens the corneal stroma due to formation of covalent bonds between collagen fibers and other molecules. Other studies documented corneal flattening and strengthening after CXL, which have halted the progression of KC and stabilized the cornea for an extended period of time.^[29-31] As such, multiple studies have reported the effects of a combined approach of ICRS implantation and CXL. For dual therapy of the combination of ICRS implantation and prophylactic CXL in patients with KC, Chan *et al.*^[32] revealed an additive effect of such a combination on Kmax and cylinder reduction. In addition, intratunnel ICRS plus CXL can induce earlier improvements in UDVA and CDVA, as well as mean K and Kmax reduction compared to epithelium-off cross-linking with ICRS implantation owing to the absence of epithelial defects.^[33] Interestingly, combining ICRS implantation and CXL in a single, same-day session can reduce keratometry values than the consecutive procedures.^[34] Seemingly, the newly dissected corneal channel created by femtosecond laser may enhance riboflavin pooling, leading to substantial corneal flattening.

On the other hand, some studies have addressed different combinations of procedures with ICRS, which are termed “triple therapy.” These studies have reported improvements in the visual acuity, as well as a reduction in refraction, corneal indices, and total HOAs.^[19,20,35-37] These favorable outcomes were significant if the procedures were performed simultaneously or sequentially. A sequential pattern involves ICRS implantation and a subsequent combination of CXL and PRK or phototherapeutic keratectomy. Mechanistically, ACXL is a stabilizing approach that provides an additional protective value to PRK in KC patients. These effects are evident if the ablation depth is not >50 μ.^[38]

In the present study, we based our work on the previously mentioned reports, suggesting that CXL performed in combination with TPRK not only halts the progression of KC but also corrects refractive errors and reduces HOAs in KC patients’ eyes that underwent ICRS implantation. We reported the effects of this triple procedure on the visual acuity, refractive outcomes, corneal indices, HOAs, and coma aberrations in moderate KC patients. We found that this approach was effective for visual rehabilitation in those patients. In the first stage, we performed ICRS implantation, which is known to flatten the corneal cone and shift the decentered corneal apex more centrally. Then after around 3 months, we conducted the second stage (TPRK and ACXL). It was thought that ICRS implantation allows implementation of TPRK with minimal tissue ablation, so we performed combined TPRK with minimal ablation and ACXL after ICRS implantation.

In this current analysis, after ICRS implantation (first stage), we indicated significant improvements in the mean logMAR UDVA and CDVA may be due to reduction in RMS HOAs and coma aberrations. Furthermore, we demonstrated a significant reduction in the mean refractive outcomes and

all corneal index values from baseline. These results agreed with the study of EL-Raggal and Tamer,^[34] who reported improvements in UDVA and CDVA along with reduction in spherical equivalent and mean keratometry values after ICRS implantation (before CXL). We also demonstrated that, after combined wavefront-guided TPRK and ACXL (second stage), there were significant improvements in logMAR UDVA and CDVA, significant reduction in the mean refractive outcomes, and reduction in all corneal indices, as compared the baseline values versus values seen after the second stage and after the first stage versus after the second stage. These results were also shown in the previously mentioned study that demonstrated an additive effect of CXL and increase in UDVA and decrease in keratometry values although they only performed a dual therapy (ICRS and CXL). Our results agreed with the study of Lee *et al.*,^[21] they concluded that the combined modality in moderate KC provided an improvement in visual acuity, all corneal indices, and HOAs. Similarly, Koh *et al.*^[26] reported that their patients have obtained satisfactory vision with no need for contact lens use; the approach was generally effective and safe for up to 12 months of follow-up.

In our study, all final parameters were significantly improved from baseline, which is also shared with other studies.^[17,35,39] The baseline logMAR UDVA was 0.5 in 22.2% of patients versus at the last followup 94.9% of patients had logMAR UDVA better than 0.5 while 27.77% had logMAR UDVA of 0 and 25% had logMAR UDVA of 0.1 [Figure 3]. The baseline logMAR CDVA was 0.2 in 44.4% of patients versus the last followup 88.9% of patients had logMAR CDVA better than 0.2 while 66.7% had (0) logMAR CDVA [Figure 4]. We observed stability in all the parameters of visual acuity, refractive errors, and coma aberration by 3 months after ACXL and TPRK. Only HOAs continued to improve until the endpoint. Contrastingly, Koh *et al.*^[26] reported stability in corneal thickness and a stable decrease in coma and spherical aberrations by 1 month and 12 months after the combined procedure, while other refractive and visual acuity indices continued to improve until 12 months. Therefore, future studies are needed with longer follow-up periods to explore the benefits of the two-stage protocol and to assess the time period during which the improvements would be expected.

In the current study, we also demonstrated a significant reduction in final RMS HOAs and coma aberrations as

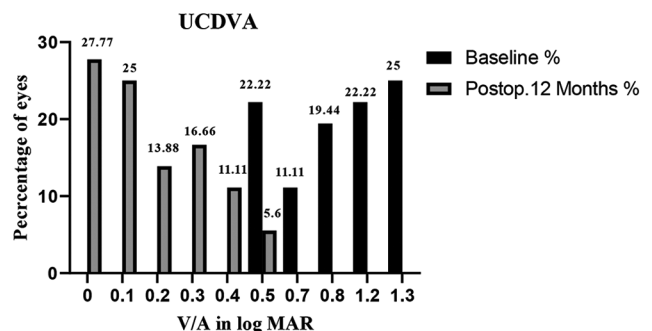


Figure 3: Uncorrected distance visual acuity percentage of eyes

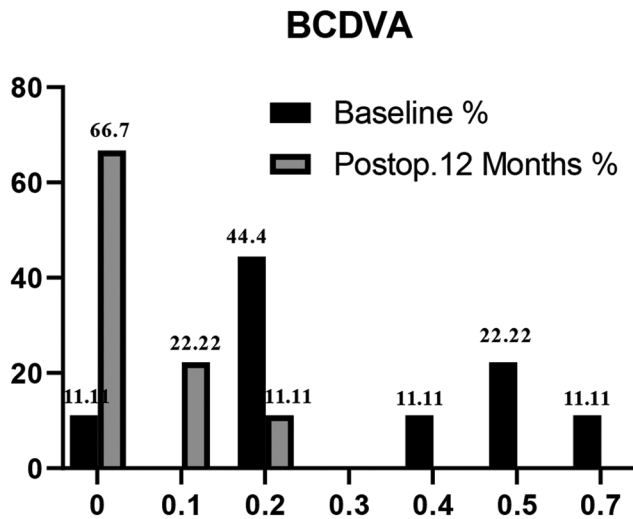


Figure 4: Corrected distance visual acuity percentage of eyes

compared to values at baseline versus after ICRS and after TPRK and ACXL, as shown in Figure 5. These results disagreed with Zeroed *et al.*,^[18] who reported that coma aberrations did not change significantly, whoever their patient's undergone different surgical technique in the form of customized topographyguided PRK + conventional CXL and Kera ring ISCR as well as coma was assessed 3 months after TGPRK and CXL. Lee *et al.*^[21] reported that 72.1% of preoperative coma aberrations were reduced at final followup from 2.47 to 0.69 μm and RMS HOAs was reduced by 62.3% from 2.87 to 1.08 μm . These results agreed with our findings, in which 72.5% of preoperative coma aberrations were reduced at final followup from 2.25 to 0.62 μm and RMS HOAs reduced by 80.5% from 3.89 to 0.76 μm . This larger reduction may be attributed to the transepithelial ablation profile. Li *et al.*^[40] reported that a fixed 55- μm TPRK ablation that we used may assist the correction of coma aberrations mostly originating in the cone area with the thinnest epithelium. On the other hand, Al-Tuwairqi and Sinjab^[17] reported a lower result where the final coma aberrations were significantly decreased compared with baseline by 37.7% reduction from 2.36 to 1.47 μm on their study of same-day topography-guided PRK and CXL after ICRS implantation in patients with low-to-moderate KC. However, they used a different technique of topography-guided PRK depending on Placido disc-derived topographic measurement, conventional CXL, and Keraring rather than our technique of corneal wavefront-guided TPRK using Schwind Sirius depending on both of Placido disc and Scheimpflug camera as well as ACXL and Intacs® SK corneal ring segments.

In terms of safety and efficacy, we noted better outcomes than other reports in the literature. Our results showed a safety ratio of 1.67 and efficacy ratio of 1.18. Lee *et al.*^[21] found safety and efficacy ratios of 0.26 and 0.89, respectively. Al-Tuwairqi *et al.*^[39] reported a ratio of 0.97 for safety and 0.88 for efficacy index. The difference might be attributable

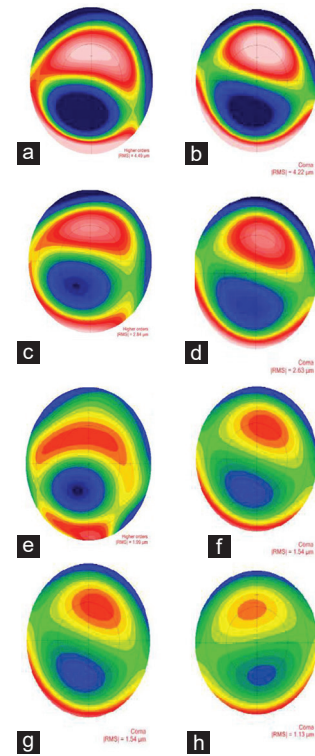


Figure 5: Sirius Schwind corneal tomography showing a representative case. (a) Baseline total HOAs: 4.49 μm , (b) Baseline coma aberrations: 4.22 μm , (c) 3 months after first-stage (ICRS) HOAs: 2.84 μm , (d) 3 months after first-stage (ICRS) coma: 2.63 μm , (e) 3 months after second-stage (TPRK + ACXL) HOAs: 1.99 μm , (f) 3 months after second-stage (TPRK + ACXL) coma: 1.54 μm , (g) 12 months after second-stage (TPRK + ACXL) HOAs: 1.85 μm , (h) 12 months after second-stage (TPRK + ACXL) coma: 1.13 μm

to a technical variation in the corneal segments, where the authors of such a study had used Keraring segments (5mm diameter) and we used thicker Intacs corneal rings with 6mm internal diameter that resulting in stronger flattening rather than the topographyguided platform used by the latter. However, similar to our study, Koh *et al.*^[26] employed a technique using Intacs segments, and they found a safety index of 2.6 and efficacy index of 1.6. The authors included a smaller number of patients and retrieved patients' data from the medical records (a retrospective design), which might imply methodological differences than our study and could partly explain the variation in the statistical estimation of safety and efficacy indices. Therefore, it is recommended to conduct a large-scale study to establish these important parameters.

Collectively, at the first stage, we performed ICRS implantation to flatten the corneal cone and shift the decentered corneal apex more centrally. Such a procedure has presumably allowed the implementation of TPRK with minimal tissue ablation. Therefore, we opted for performing a combined TPRK and ACXL with minimal ablation after ICRS implantation. However, we experienced some limitations in the current analysis. First, the relatively small number of patients who were eligible for inclusion might influence the robustness

and the statistical power of the outcomes, particularly the parameters indicating stabilized visual acuity, refraction, and corneal indices. It is therefore imperative to carry out future studies based on sample sizes estimated via power analyses to exclude the lack of a causal association in distinct instances. Second, the lack of a control group to which the obtained results could be compared might limit the appropriate comparison of the added benefits of ACXL + TRPK following ICRS to other combined/single approaches. This might be compensated via conducting well-designed controlled clinical trials. Finally, the continually improving parameters of visual rehabilitation until the endpoint of the study might underscore the need to explore the long-term outcomes of such a “triple therapy.”

CONCLUSIONS

A combination of corneal wavefront-guided TRPK and ACXL after Intacs ICRS implantation was a feasible option for improving visual acuity, correcting mild refractive errors, reducing corneal indices, and correcting HOAs and coma aberrations in moderate progressive KC patients up to 1 year. The current study supports the previous evidence regarding the benefits of such a two-stage, triple approach. Nevertheless, within the established limitations, we recommend conducting well-designed, prospective randomized clinical trials with a control arm, considering the recruitment of larger sample sizes and investigating KC patients over longer periods of time.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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