Embase (Elsevier)

ORIGINAL ARTICLE

Combined Corneal Collagen Cross-linking and Mini Asymmetric Radial Keratotomy for the Treatment of Keratoconus

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Article Information

Received: 06 Jul 2015
Accepted: 18 Sep 2015
Plagiarism software: Turnitin

Keywords:
Keratoconus,
Cornea,
Mini asymmetric radial keratotomy,
Corneal collagen cross-linking

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ABSTRACT

Objective: The primary objective of this study was to quantify the visual improvement and the reduction of corneal curvature achieved through association of Mini Asymmetric Radial Keratotomy (MARK) and Corneal Collagen Cross-linking (CXL).
Design: Retrospective clinical trial.
Methods: Sixteen eyes (sixteen patients) were included. Computerized corneal topography and Scheimpflug camera equipment were used to measure higher order corneal aberrations before treatment and during follow-up. Outcome parameters, including uncorrected visual acuity and best corrected visual acuity, have been measured as well. Examinations were performed at 3, 6, 12 and 24 months following both MARK and CXL.
Results: A sharp reduction of both corneal curvature and corneal aberrations was observed after MARK surgery, followed by a smaller improvement following CXL treatment.
Conclusion: The combination of MARK with CXL offers a significant improvement of visual acuity and a reduction of corneal curvature along with the corneal reinforcement provided by CXL.

INTRODUCTION

Keratoconus (KC) is a corneal ectatic disease that results in bilateral and asymmetrical corneal distortion, altered refractive powers, and reduced vision. KC becomes manifest during the second decade of life and during puberty, and it progresses over 10 to 20 years until the degeneration gradually reduces.

Treatments for keratoconus depend on both the severity and the rapidity of its progression. In the most advanced cases of keratoconus, corneal transplantation is frequently performed, especially Penetrating Keratoplasty (PK), although statistical studies have shown that the mean survival of corneal grafts is 16.88 years,[1] meaning that a number of young patients undergoing PK may have to repeat the procedure during their lifetime. However, the need for corneal grafting may be delayed or even avoided if keratoconus is diagnosed in early stages, due to a number of conservative treatments for the disease.

Conservative surgical techniques include Asymmetric Radial Keratotomy (ARK),[2] Mini Asymmetric Radial Keratotomy (MARK),[3] Circular Keratotomy[4] and Intrastromal Corneal Ring Segments (ICRS).[5] These techniques address the refractive defects of keratoconus by reducing corneal curvature and effectively increasing visual acuity.

Another original technique recently developed is Corneal Collagen Cross-linking (CXL), a procedure that directly addresses the intrinsic structural weakness of the cornea.[6] Although CXL treatment was primarily aimed at reinforcing the corneal stroma and stopping keratoconus progression, a slight improvement of visual acuity has been reported following treatment. The

Access this article online	
Website: www.actamedicainternational.com	Quick Response code
DOI: 10.5530ami.2016.1.14	

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increase of visual acuity quantified in the Dresden studies was 1.4 snellen lines.

We have successfully performed CXL since 2005, alone or combined with other refractive procedures, including PRK and Phakic Intraocular Lens implantation. This study, however, focuses on the outcomes of combined Corneal Collagen Cross-linking (CXL) with Mini Asymmetric Radial Keratotomy (MARK) in patients affected by keratoconus.

The combination of MARK surgery and CXL treatment aims to address visual problems of keratoconic patients, while the purpose of this paper is to quantify both the visual improvement and the reduction of corneal curvature achieved by the association of MARK surgery and CXL treatment.

The rationale for the combination of these procedures was that no contraindicating factors were identifiable, along with the fact that each technique focuses on a different aspect of the disease. CXL acts at the microscopic level and influences corneal structural strength by increasing molecular links between the parallel stromal collagen layers, while MARK produces a localized reduction of corneal curvature that effectively reduces the corneal bulging of the area affected with keratoconus.

MATERIALS AND METHODS

Clinical selection excluded eyes with less than 400 microns of corneal thickness on the apex of the cornea or more than 60 D of corneal curvature, as well as patients with any chronic or recurrent ocular infections, while careful evaluation of patients affected with other systemic or ocular diseases was taken into account. Patients were thoroughly informed of all general aspects concerning their condition, including various alternative treatment possibilities, following which they were briefed about the combined treatment, including expected visual and clinical outcomes and possible treatment risks. Patient informed consent was always required.

16 eyes of 16 patients were included, although more patients have undergone the combined protocol with less than 24 months follow-up. Mean age of patients was 37 years (range 24 to 50) and all patients were contact lens intolerant. MARK was performed at least 24 months before CXL. Follow-up data collection was performed retrospectively and set at 24 months for both procedures. Complete MARK incision consolidation was considered an absolute pre-requisite inclusion criterion and CXL treatment was applied only after complete consolidation of the corneal incisions was observed with slit lamp bio-microscopy.

All patients underwent a thorough clinical examination before each treatment, which included measurement of uncorrected (UCVA) and best corrected visual acuity (BCVA), computerized corneal topography, axial biometry, pachymetry, endothelial cell count, keratometry, scheimpflug camera corneal analysis and slit lamp examination.

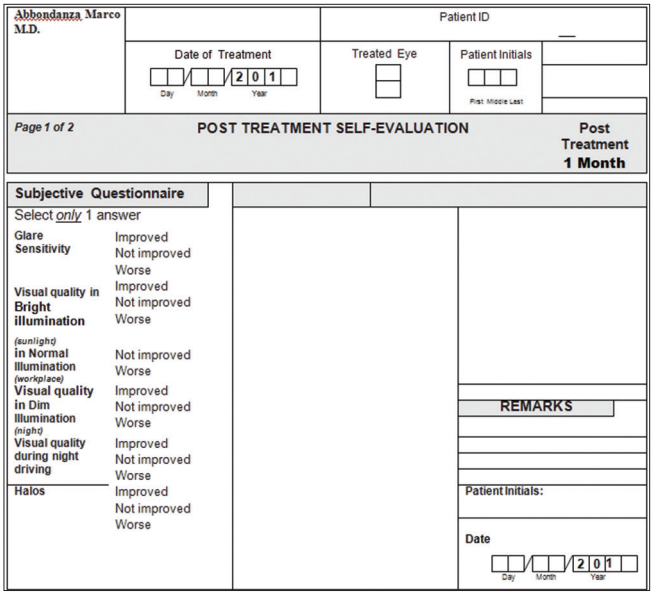
Post-MARK and post-CXL follow-up was performed at 3, 6, 12 and 24 months following treatment and consisted in clinical and functional examination, along with the measurement of higher order aberrations.

We used computerized corneal topography (CSO Focus Topographer/eyetop software- Scandicci, Italy) and scheimpflug camera equipment (Pentacam - Oculus optikgerate- GmbH, Wetzlar) to measure higher order corneal refractive aberrations before treatment and during follow-up.

The assessment of the subjective variations of visual performance reported by the patients was performed by asking each of them to complete our own subjective visual evaluation questionnaire (SVEQ) at 3, 6, 12 and 24 months following each procedure. This was done in order to better evaluate post-operative quantitative data with more qualitative post-operative information (Figures 1 and 2).

MARK SURGERY

Preparation for MARK surgery started by devising its surgical plan. Factors that were carefully considered included the designation of the corneal clear zone, which was to be left as large as possible, along with the determination of the number, position, length and depth


Abbondanza Marco M.D.

Patient ID

Date of Treatment Day Month 2 0 1 Year

Treated Eye

Patient Initials First Middle Last

Page 1 of 2

POST TREATMENT SELF-EVALUATION

Post Treatment 1 Month

Subjective Questionnaire

Select *only* 1 answer

Glare Sensitivity	Improved / Not improved / Worse
Visual quality in Bright illumination (sunlight)	Improved / Not improved / Worse
in Normal Illumination (workplace)	Not improved / Worse
Visual quality in Dim Illumination (night)	Improved / Not improved / Worse
Visual quality during night driving	Improved / Not improved / Worse
Halos	Improved / Not improved / Worse

REMARKS

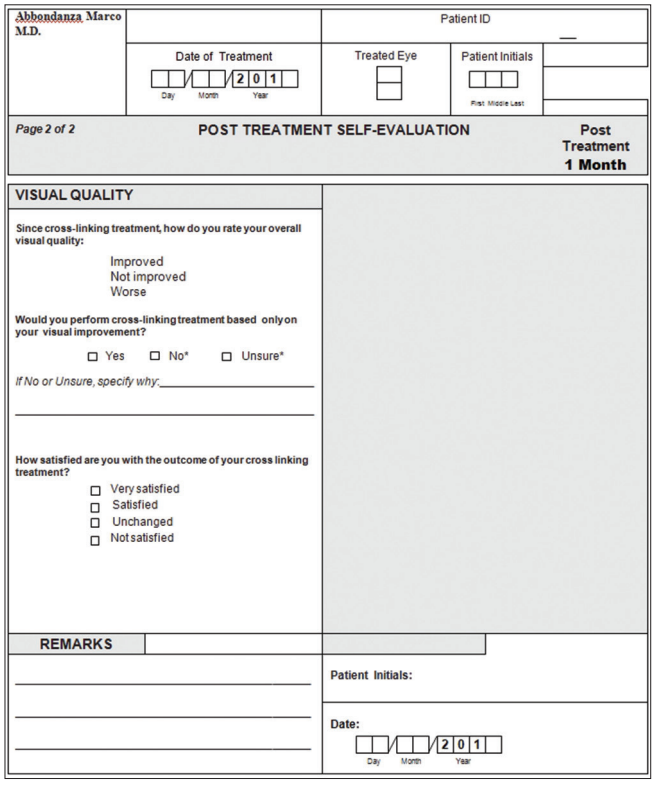
Patient Initials:

Date Day Month 2 0 1 Year

Figure 1: Customized questionnaires used to evaluate the MARK + CXL combined protocol (page 1)

of the micro-incisions performed with a diamond knife. Incisions designed during the surgical plan were marked on a copy of the corneal topography print and used as a surgical reference during the procedure. The target refractive result was determined at the end of this pre-operative decision process.

Corneal incisions were performed with particular attention to the irregularity of corneal thickness, especially along the steepest axis of astigmatism, while in no case incisions were extended beyond a 8mm corneal diameter. This precaution was necessary in order to conserve a valid corneal margin in case a Penetrating Keratoplasty should be required in the future. Custom made double concentric corneal markers were used to create two concentric circular indentations on the cornea, in order to limit the central and peripheral ends of the incisions to a maximum of 7.5-8mm on the external end and a minimum of 3.5-4mm on the internal end. Incisions performed with MARK surgery are very different from those adopted in standard Radial Keratotomy (RK), mainly due to the fact that they are much shorter (approximately 2mm) and involve a limited angular span of the corneal area. The result is a localized reduction of corneal curvature in the area of the cornea affected by keratoconus and the achievement of a much higher corneal stability compared to that of RK (Figure 3).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Patient ID

Date of Treatment ☐☐/☐☐/2 0 1 ☐ (Day / Month / Year)

Treated Eye ☐

Patient Initials ☐☐☐ (First Middle Last)

Page 2 of 2

POST TREATMENT SELF-EVALUATION

Post Treatment 1 Month

VISUAL QUALITY

Since cross-linking treatment, how do you rate your overall visual quality:

Improved
Not improved
Worse

Would you perform cross-linking treatment based only on your visual improvement?

☐ Yes ☐ No* ☐ Unsure*

*If No or Unsure, specify why:*_____

How satisfied are you with the outcome of your cross linking treatment?

☐ Very satisfied
☐ Satisfied
☐ Unchanged
☐ Not satisfied

REMARKS

Patient Initials:

Date: ☐☐/☐☐/2 0 1 ☐ (Day / Month / Year)

Figure 2: Customized questionnaires used to evaluate the MARK + CXL combined protocol (page 2)

CXL TREATMENT

We performed CXL treatment according to the standard Dresden procedure. Topical anesthesia was applied prior to the treatment with benoxinate chloride 0.4% drops. The removal of corneal epithelium was performed using an ophthalmic scalpel (MicroFeather; Feather Safety Razor Co., Ltd., Osaka, Japan) and a surgical microscope. During the procedure the eyelids were kept open using surgical forceps.

The riboflavin solution was applied 30 minutes before UVA application, 10 times at 3-minute intervals. Riboflavin was then applied six times at 5-minute intervals during UV-A application, with a total UV-A exposure time of 30 minutes. The UVA source used was the UV-X illumination system version 1000, from IROC AG, Switzerland.

Following the treatment, a contact lens was placed and topical antibiotics and non steroidal anti-inflammatory drops were prescribed. Clinical examination was performed on the following day. The contact lens was removed three days after CXL, while corneal epithelial healing was checked.

RESULTS

As expected from a refractive procedure used in the treatment of several hundreds of patients, MARK produced a significant correction of the refractive error of the cornea. Following CXL, no untoward reactions were observed, except a slight corneal haze that was assessed at slit lamp observation. Haze and corneal epithelium irregularity temporarily affected visual acuity in the immediate post-

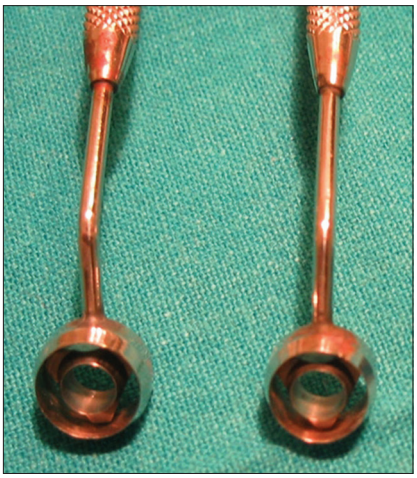

Figure 3: Custom made double concentric corneal markers adopted to mark\ indent the inner and outer limits for MARK incisions. Note that various diameters exist but inner 3.5\outer7.5mm is the most used. The outer diameter must be chosen to provide a safe margin in case of future Penetrating Keratoplasty (maximum 7.5mm) while the inner diameter must be adequate to limit incisions from reaching into the central optical zone of the cornea

treatment period. Corneal curvature decreased in all treated eyes following MARK treatment in direct proportion to the number, length and depth of incisions, as planned. Reduction of corneal curvature was observed also following CXL, to a lesser extent.

Specifically, corneal curvature decreased from an average pre-MARK value of 48.5 dioptres (range 44.25-53.25) to a post-MARK value of 43.60 dioptres (range 39.25-48.5).

A the end of the 24-month post-MARK follow-up, a reduction of higher order refractive aberrations was observed as well. Specifically, astigmatic aberrations decreased from an average 4.8µm (range 2.8-6.9) to 2.1µm (range 1.8-3.8). Trefoil decreased from an average 1.5µm (range 0.6-2.7) to 0.7µm (range 0.4-1.7). Coma decreased from an average 5.4µm (range 3.7-6.2) to 3.1µm (range 2.0-3.5). 24 months after MARK surgery, mean uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) increased respectively by an average 3.1 and 1.3 snellen lines.

Corneal curvature then further decreased from an average pre-CXL value of 46.20 dioptres (range 41.25-49) to a post-CXL value of 44.8 dioptres (range 40.5-47.5). A the end of the 24-month post-CXL follow-up, astigmatic aberrations decreased from an average 2.0µm (range 1.6-4.0) to 1.8µm (range 1.2-3.6). Trefoil decreased from an average 0.8µm (range 0.5-2.0) to 0.6 µm (range 0.4 -1.4). Coma decreased from an average 3.3µm (range 2.0-3.8) to 2.7µm (range 1.8-3.4). 12 months after CXL, mean uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) increased respectively by an average 0.8 and 1.1 snellen lines.

Patients treated with combined MARK surgery and CXL treatment reported a considerable improvement of visual quality, as assessed by our customized subjective visual evaluation questionnaires. As expected, the most appreciable visual improvement related to the post-MARK period was reported early in the follow-up (within 3 months). On the other hand, the subjective visual improvement following CXL was slight and was observed later in the follow-up (6-12 months) (Figures 4 and 5, Table 1)).

DISCUSSION

The combination of MARK surgery with CXL treatment in our patients was uneventful and, moreover, corneal

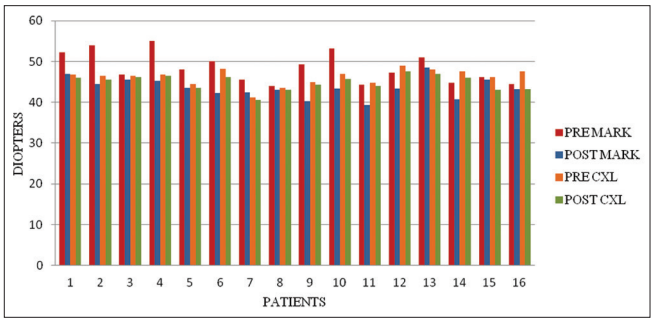

Figure 4: Keratometric variation following MARK and CXL

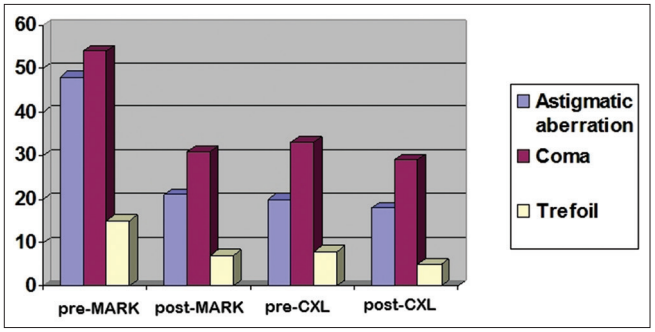

Figure 5: Variations in corneal aberrations following MARK and CXL

Table 1: Keratometric variation following MARK and CXL

Pre-MARK (Km)	Post-MARK (Km)	Pre-CXL (Km)	Post-CXL (Km)
48.5/56 (52.25)	44.5/49.5 (47)	44.75/49 (46.87)	44/48 (46)
52.5/55.5 (54)	44/45 (44.5)	45/48 (46.5)	43.75/47.25 (45.5)
46.25/47.25 (46.75)	45/46 (45.5)	46/47 (46.5)	46/46.5 (46.25)
54/56 (55)	44.5/46 (45.25)	45.5/48 (46.75)	45.5/47.5 (46.5)
46/50 (48)	41.5/45.5 (43.5)	42.5/46.5 (44.5)	42/45.5 (43.5)
45.5/54.5 (50)	38.25/46.25 (42.25)	44/52.5 (48.25)	43/49.5 (46.25)
43/48 (45.5)	40.5/44.5 (42.5)	39/43.5 (41.25)	39/42 (40.5)
43/45 (44)	42/44 (43)	42.5/44.5 (43.5)	42/44 (43)
46/52.5 (49.25)	39.5/41 (40.25)	43/47 (45)	43.5/45 (44.25)
51.5/55 (53.25)	42.5/44.25 (43.37)	45.5/48.5 (47)	44/47.5 (45.75)
42/46.5 (44.25)	37.5/41 (39.25)	43.5/46 (44.75)	42/46 (44)
42/52.5 (47.25)	38.25/48.5 (43.37)	48.5/49.5 (49)	47/48 (47.5)
49/53 (51)	47/50 (48.5)	47/49 (48)	46/48 (47)
42.5/47 (44.75)	38.5/43 (40.75)	45/50.25 (47.62)	44/48 (46)
45/47.25 (46.25)	44.5/46.5 (45.5)	44.5/48 (46.25)	41/45 (43)
42/47 (44.5)	41.5/45 (43.25)	43.5/51.5 (47.5)	40/46.5 (43.25)

reaction to CXL in eyes previously treated with MARK did not differ from eyes treated with CXL alone. Our customized questionnaires, employed to assess subjective patient satisfaction, shown that visual quality was greater in patients treated with the combination protocol, compared to that of CXL treatment alone.

Quantitative improvement of visual acuity was also superior in the combined treatment protocol, a condition that was entirely predictable, due to the fact that MARK surgery applies customized refractive correction to patients which results in immediate visual improvement, something that is not achievable when CXL alone is performed. In order to better evaluate our results, we also compared them to those of combined CXL with Intracorneal Ring Segments (ICRS),[5,7] which show that the refractive outcomes of ICRS are significant. We believe, however, that MARK surgery is a more versatile option, mainly due to the fact that refractive results can be revised by increasing the number, length or depth of the micro-incisions. Revision of unsuccessful ICRS procedure is also possible, although it involves removal and reinsertion of new ICRS.

The rationale for the combination of Mini Asymmetric Radial Keratotomy with Corneal Collagen Cross-linking was that the combination protocol could supply both a refractive and a reinforcing result. Accordingly, MARK is conceived as refractive procedure and CXL as a reinforcing treatment. When combined with CXL, MARK contributes to the decrease of corneal bulging through localized flattening of corneal shape and reduction of corneal curvature, which is then further stabilized by CXL.[8]

It is important to note, moreover, that the differences between MARK incisions and Radial Keratotomy (RK) incisions are extremely significant when treating KC. They are mainly:

1) Micro-incisions performed with MARK are very short (approximately 2mm) in comparison to incisions adopted in Radial Keratotomy. RK longer incisions might also influence a future PK procedure, as opposed to MARK micro-incisions, which are also less deep than those of RK;
2) Micro-incisions involve a limited angular span of the cornea compared to the full span of RK incisions; resulting in a higher corneal stability of MARK surgery over time, something that cannot be obtained with RK.

The main disadvantage of MARK is that it is a "custom" refractive procedure, which represents a known limit to the adoption of routine techniques by ophthalmic surgeons, due to the fact that visual outcome will be certainly influenced by specific surgical skills and specific patient selection.

CONCLUSION

MARK surgery combined with CXL treatment can offer a significant improvement of visual acuity and a reduction of corneal curvature-astigmatism, along with the corneal reinforcement provided by CXL.[9] It is a valid therapeutic option for selected patients that are contact lens intolerant and have inadequate vision with spectacles, due to high irregular astigmatism.

This indication can be extended to selected patients that are especially prone to develop superficial and centrally located corneal scars secondary to extended contact lens use.

Most importantly, the short incisions used in MARK do not limit future surgical treatment such as Penetrating Keratoplasty, because micro-incisions do not extend beyond a corneal diameter of 8mm peripherally, which means that MARK incisions are included in the diameter of corneal tissue to be removed and substituted with the corneal graft.

In conclusion, the availability of new treatments for keratoconus that effectively stop the evolution of corneal deformation, has changed the therapeutic approach to the disease. It is worth to remind that the disease can be insidious, especially when it develops mono-laterally and in early adolescence. Application of Corneal Collagen Cross-linking with epithelium removal, in these cases, may arrest debilitating reduction of vision and avoid the need for further treatment.[10] In this context, the importance of an early diagnosis of keratoconus, by adoption of adequate screening procedures, cannot be overstressed.

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How to cite this article: Abbondanza M, Abdolrahimzadeh B, Guidobaldi M. Combined corneal collagen cross-linking and mini asymmetric radial keratotomy for the treatment of keratoconus. Acta Medica International. 2016;3(1):63-68.

Source of Support: Nil, **Conflict of Interest:** None declared.