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Original Article

In Vivo Confocal Microscopy Findings After Anterior Stromal Puncture in the Treatment of Recurrent Corneal Erosion Syndrome

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Abstract

Objectives: The objectives of the study are to show up the healing processes after anterior stromal puncture (ASP) in the cornea using *in vivo* confocal microscopy (IVCM) and to investigate the efficacy of ASP in the treatment of recurrent corneal erosion (RCE).

Methods: This is a prospective, non-randomized, consecutive series. Twenty-three eyes of 19 patients diagnosed with RCE were evaluated between March 2020 and January 2022. Outcome measures included age, sex, laterality, etiology of RCE, duration and recurrence of symptoms, additional treatments required, and complications. IVCM was performed on the same day, at 1st week, 1st, and 6th month.

Results: Mean age was 41.5±11.3 years, 63.2% of patients were female and 65.2% of eyes had unilateral involvement. Corneal trauma (56.5%) was the most common cause. Mean follow-up was 21.1 months (range 8–33). At the final follow-up, 69.5% of eyes were symptom free, 17.4% required a second ASP, and 13% needed a third ASP. At the 1st week, the epithelium became intact. An increase in activated keratocytes and dendritic cells (DCs) with beading of nerve fibers was observed. At 1st month, DCs and activated keratocytes were still present. At the 6th month, a scar was left. The superficial and basal epithelial cell formation and subbasal corneal nerve plexus returned to normal.

Conclusion: IVCM has a superiority in visualizing cornea at cellular level. After ASP which is a safe, practical, and cost-effective treatment option in paracentral or peripherally located RCE, IVCM may help the surgeon to better observe and understand the post-healing processes and explain the recurrences.

Keywords: Anterior stromal puncture, Dendritic cells, *In vivo* confocal microscopy, recurrent corneal erosion, subbasal corneal nerve plexus

Introduction

Recurrent corneal erosion (RCE) is a chronic disease of the cornea epithelium characterized by multiple sudden onset of pain, occasionally on first awakening. Blurred vision, photophobia, redness, and tearing are the common accompanying symptoms. The classification of the etiologies of RCE is divided into two subheadings: Primary and secondary. The intrinsic factors such as corneal dystrophies

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are summarized as primary, and the acquired conditions such as trauma, degeneration, eyelid pathologies, following ocular infection of refractive surgery, and systemic causes are summarized as secondary (1). Among all those reasons, in 45%–64% of reported cases, mechanical trauma is the most common cause, while epithelial basement membrane dystrophy (EBMD) is the second most common cause with a ratio of 19%–29% (2). Conservative approach consisting of artificial tears, antibiotic drops, and hypertonic sodium chloride ointment is widely applied for the treatment. In unresponsive cases, blood serum drops, (1) soft bandage contact lens (BCL), (3) oral matrix metalloproteinase inhibitors, (4) or corticosteroids (1) take place in the treatment. In patients who failed conservative therapy, surgical procedures including anterior stromal puncture (ASP), (5) neodymium-doped yttrium-aluminum-garnet laser, (1,2,6) superficial keratectomy, (1,2) or phototherapeutic keratectomy (PTK) (6,7) are required.

ASP was first used in the treatment of RCE in 1986 by McLean et al.(8) and comparative studies have been conducted to evaluate the effectiveness of this procedure, alone or in combination with other treatment options (5, 9-11). Despite successful reports of ASP for RCE, the mechanism of how the procedure works on the cellular level is still unknown, and there are only few reports on the process of healing with ASP; a study reported in 1990 investigated the healing process after ASP by electron microscopy in rabbit corneas with recurrent erosion (12). In that study, the authors found that basement membrane reproduction occurred much more rapidly after ASP compared to microdiathermy, which is a destructive process, speculating that this was a result of immediate exposure of corneal epithelial cell to type I collagen, as a wound healing response. Although electron microscopy can show the ultrastructure, it has some handicaps in imaging living tissue. Since it has been shown that human corneal nerves begin to deteriorate after the first 14 h of death, (13) electron microscopy was abandoned because of the time needed for preparation the tissue before imaging.

Heidelberg Retina Tomograph II–Rostock Cornea Module (HRTII-RCM) (Heidelberg Engineering, Heidelberg, Germany) provides the highest resolution of corneal images (14) and still has the superiority in real-time cross-sectional non-invasive imaging.

However, as far as our knowledge, a study showing confocal microscopy findings of cornea after ASP in patients with RCEs has not been published yet. In this first study, it was aimed to demonstrate the healing processes after ASP in the cornea using IVCM and to investigate the efficacy of ASP in the treatment of RCE.

Methods

Twenty-three eyes of 19 patients diagnosed RCE between March 2020 and January 2022 were included. The main outcome measures of the study were determined as age and gender, laterality, etiology of RCE, the duration and recurrence of exhibiting symptoms, additional treatments necessitated, and intra and post-procedure complications. The study was approved by the institutional review board (IRB) of Koç University Committee on Human Research (No: 2021.320.IRB1.146) in the light of the tenets of the declaration of Helsinki.

Surgical Procedure

Following topical 0.05% proparacaine eye drops (Alcaine®; Alcon, Texas, USA) application, ASP was performed on the slit lamp. The patient was seated in the same position as is in the routine ophthalmologic examination. The tip of a 27-gauge needle, bent with a needle holder, was positioned at 90° toward the corneal surface to notch the affected lesion and was used to create nearly 15–30 confluent stromal micropunctures. The number of micropunctures to be made was determined according to the area of RCE <1 mm apart (Fig. 1).

IVCM

The IVCM was done on the same day, 1st week, 1st month, and 6th month after the ASP using HRTII-RCM (Heidelberg Engineering, Heidelberg, Germany) which presents a higher magnification up to 800 fold (15). The therapeutic lens, if any, was removed before imaging and a drop of gel (Recugel ophthalmic ointment; Bausch and Lomb, Berlin, Germany) was put on the ocular surface and inside of the TomoCap (Heidelberg Engineering GmbH, Heidelberg, Germany) as well. After installation of topical anesthetic eye drop (0.05% Proparacaine, Alcaine®; Alcon, Texas, USA), corneal lesions were examined by applanating TomoCap and the findings were recorded with a series of corneal images with 1-micron scanning steps. The images were captured from epithelium, Bowman's layer, anterior, and mid-stroma.

Instantaneously following the first IVCM imaging, the therapeutic BCL was applied, and topical 0.5% moxifloxacin eye drops (Vigamox®; Alcon, Texas, USA) and 0.15% sodium hyaluronate eye drops (Thealoz Duo®; Thea, Clermont-Ferrand, France) 4 times daily were prescribed. At the 1st week visit, BCL was removed off, and only preservative free artificial tears were recommended.

Statistical Analysis

The statistical analysis was done through SPSS statistical software version 22 (SPSS, Inc., Chicago, IL, USA.). The values were reported as mean±standard deviation (SD) or shown in percentage (%).

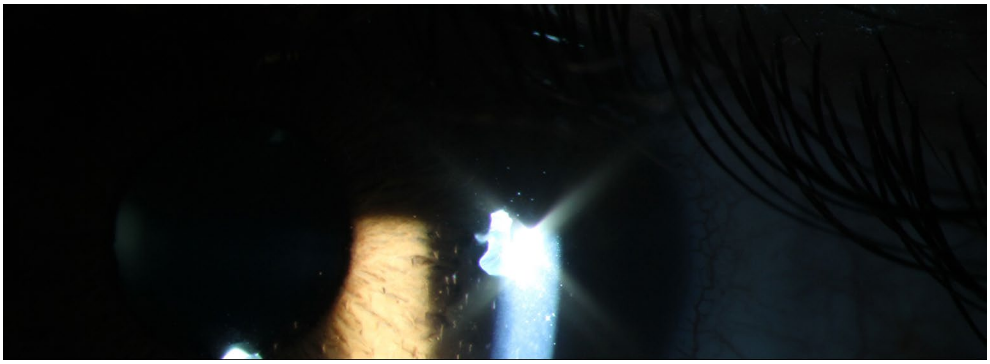

Figure 1. Immediately after anterior stromal puncture, the biomicroscopic view of post-procedure punctures.

Results

The mean age of patients was 41.5 years (±9.3 SD). The 63.2% percentage of patients (12/19) were female and 36.8% (7/19) were male. The biomicroscopic findings were unilateral in 15 eyes (65.2%) and were bilateral in 8 eyes (34.7%). While 13 of 23 eyes (56.5%) had a history of prior trauma, 6 eyes (26%) had map-dot-fingerprint dystrophy, 2 eyes (8.7%) had laser-assisted in situ keratomileusis (LASIK) surgery, and 2 eyes (8.7%) did not have any significant ocular history (e.g., prior refractive surgery or existence of other ocular comorbidities). The mean duration of symptoms was 8 months (±11.7 SD). The mean number of recurrences of exhibiting symptoms was 2.7 (±1.3 SD) before ASP. All the patients had prior history of lubricant eye drops and BCL use. The mean follow-up was 21.1 months (±5.8 SD), and all the patients had a minimum of 8-month follow-up.

During the follow-up, 16 of 23 eyes (69.5%) were completely symptom free and no further surgical treatment was required. The ASP was repeated in case of no improvement after a month. The second ASP was performed in 4 eyes (17.4%), 2 of which had previous trauma history, 1 of which had map-dot fingerprint dystrophy, and 1 had previous LASIK surgery. Unfortunately, a third ASP was repeated in 3 eyes (13%). Two eyes with previous corneal trauma and the eye with map-dot-fingerprint dystrophy ended up with the third ASP. No patient was needed superficial keratectomy or PTK. No haze or any sign of infection or any post-procedure complication was observed.

The punctures extending anterior stroma, i.e., needle entry points were clearly seen immediately after ASP (Fig. 2). The hyperreflective boundaries of the punctures and surrounding hyper-reflective microdots were observed. The reflectivity and branching of long nerve fiber bundles were found to be reduced and the fibers were found to be thinned. In addition, the nerve fibers were seen in parallel course showing a sparse distribution. In stroma, no significant finding was found. These findings were seen in all study patients without exception with minimal differences.

1 week later, it was seen that the epithelium was intact, and the defect was beginning to be fulfilled. The hyper-reflective and granular deposits around the puncture site were imaged, as well as the increase in dendritic cells (DCs) and beading formation of nerve fibers. The activated keratocytes in anterior stroma were also seen (Fig. 3).

At 1st month, the healing was almost completed in all patients, and the distinction of the puncture site was difficult to distinguish at the level of epithelium. Deep into the basal cell layer, the hyper-reflective boundaries surrounded with many DCs were observed. The activated keratocytes were still visible in anterior stroma (Fig. 4).

At 6th month, scar formation was visible on both slit lamp and IVCM. The superficial and basal epithelial cell formation was improved. The corneal subbasal nerve plexus tended to be recovered with mild-to-moderate DC infiltration. The keratocyte activity in anterior stroma was returning to normal (Fig. 5).

Out of our study design, in a patient who had three attacks in 10 months before ASP, we observed that these IVCM findings persisted dramatically until the 2nd month. At the 1st week, the hyper-reflectance located on the healed puncture site and the increase in DCs and activated keratocytes were observed. In addition, at the 2nd week, the corneal subbasal nerve fiber bundles were visualized parallel to each other with reduced branching and reflectivity. The activated keratocytes were present in the anterior stroma. Those findings persisted dramatically until the 2nd month as well. In the IVCM images of another patient who had a prior LASIK surgery, the scar formation left by the puncture, an increase in tortuosity of nerve fiber bundles and a decrease in branching were observed similarly even 2 years after ASP. The persistence of activated keratocytes in shallow anterior stroma was also demonstrated.

Although the mean follow-up was 21 months, all patients had undergone their last confocal scanning at the 6th month of follow-up, both due to study design and because some patients had a limited follow-up of less than a year.

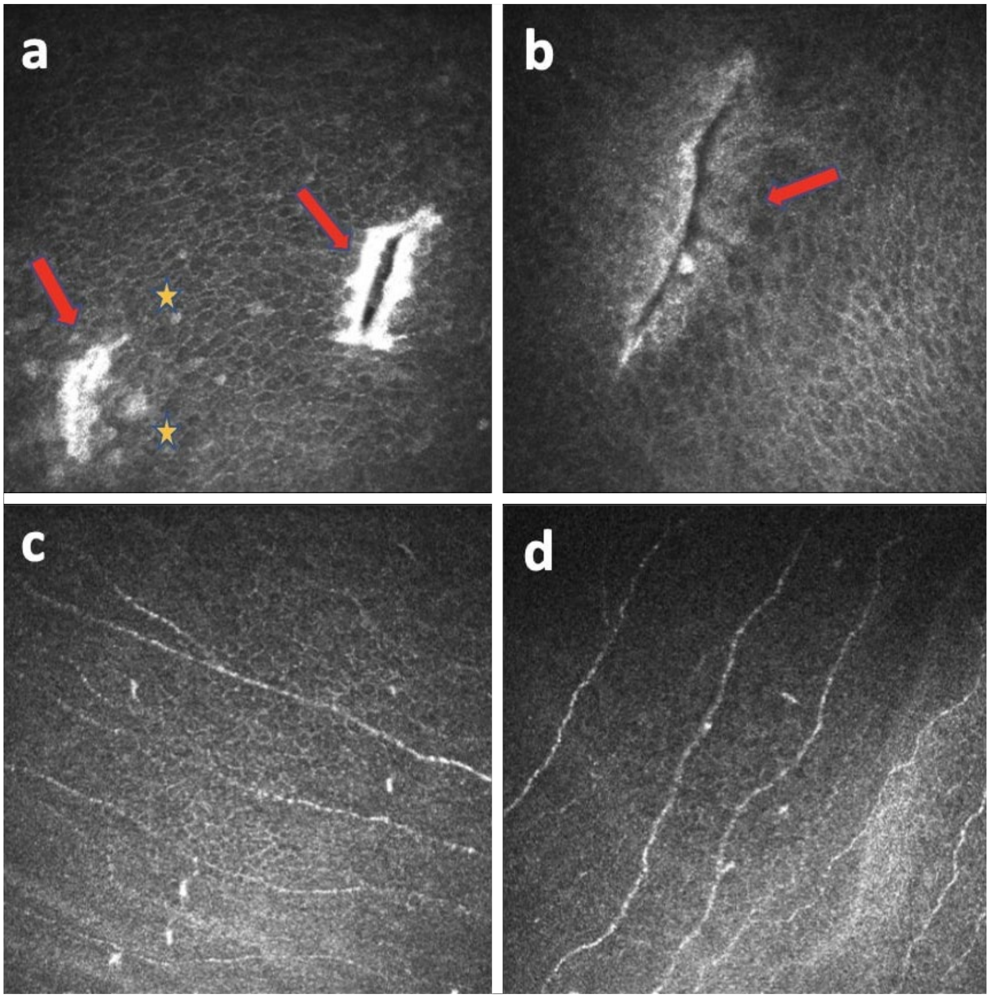

Figure 2. In vivo confocal microscopy images immediately after anterior stromal puncture in corneas of two different patients with recurrent corneal erosion. **(a and b)** A needle entry point (red arrows) of the puncture extending anterior stroma and its hyperreflective boundaries with surrounding hyper-reflective microdots (yellow stars) was clearly seen in the patients. **(c and d)** The decrease in reflectivity and branching of long nerve fiber bundles and thinning in fibers were observed, and in addition, the parallel course of nerve fibers showing a sparse distribution was conspicuous.

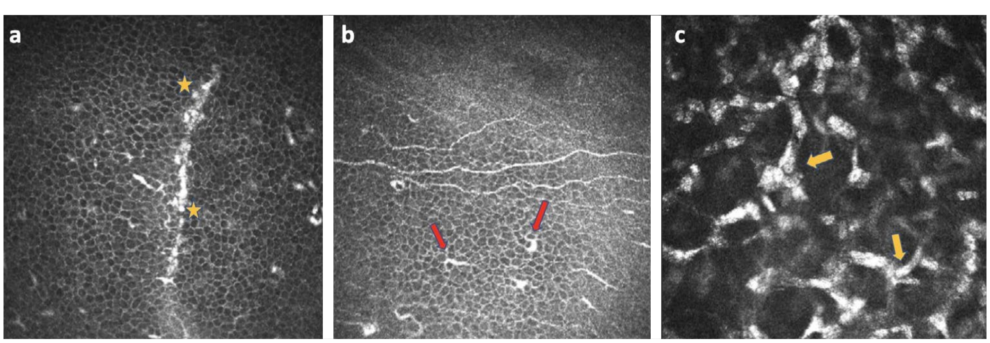

Figure 3. In vivo confocal microscopy images at 1st week after anterior stromal puncture in a patient who had a history of corneal trauma 6 months ago before recurrent corneal erosion diagnosis. **(a)** The epithelium was seen intact, and the defect was beginning to be fulfilled accompanying hyper-reflective and granular deposits (yellow stars) placed around the puncture site. **(b)** Increased number of dendritic cells (red arrows) and beading formation of nerve fibers were imaged. **(c)** The activated keratocytes (yellow arrows) were seen in anterior stroma.

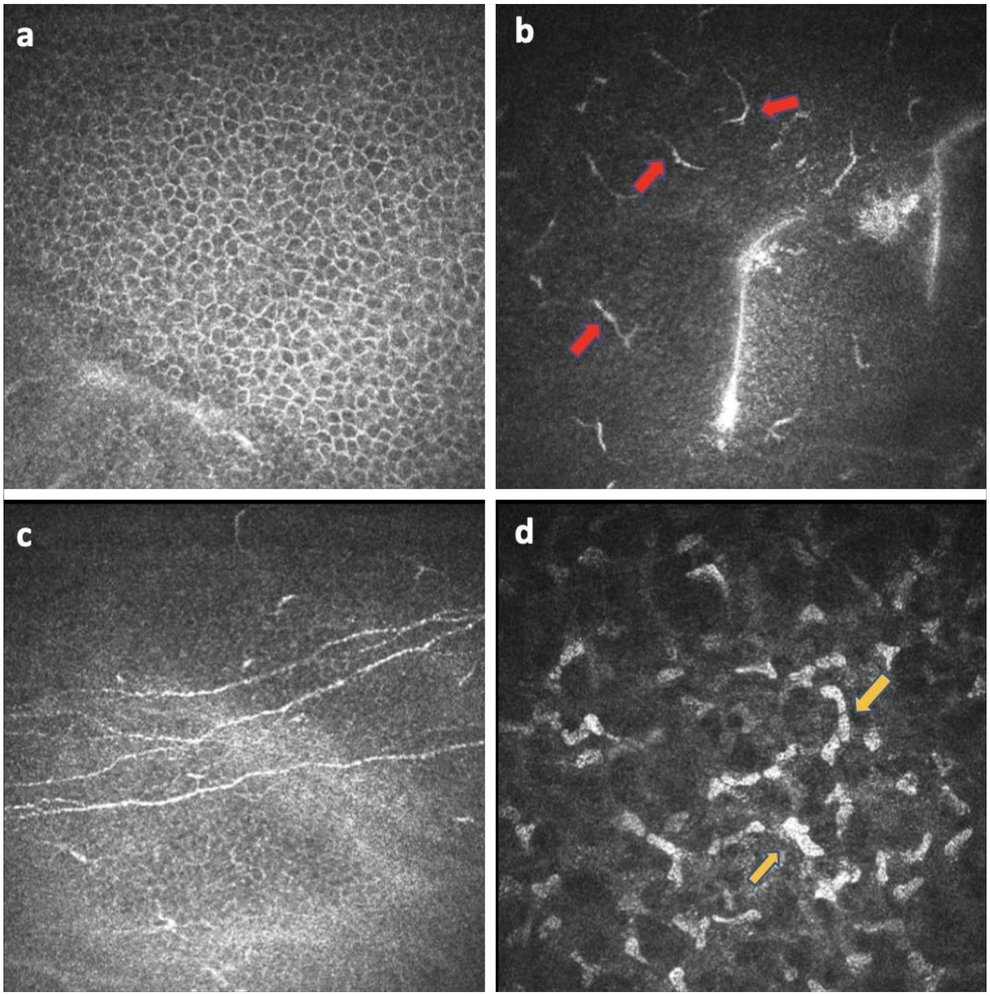

Figure 4. In vivo confocal microscopy images at 1st month after anterior stromal puncture in a patient who had a history of ocular trauma 5 months ago before recurrent corneal erosion diagnosis. **(a)** At the level of the epithelium, the healing was completed, and the boundaries of the puncture site became almost indistinguishable. **(b)** Into the deeper, hyper-reflectivity was observed at the puncture site surrounded by dendritic cells (red arrows). **(c)** It was seen that the reflectivity and branching of nerve fiber bundles were slightly increased and **(d)** the activated keratocytes were still present in anterior stroma (yellow arrows).

Discussion

Our study of IVCM imaging in 23 eyes of 19 patients who underwent ASP for the treatment of RCE showed that there is a significant increase in DCs starting in the 1st week that prevails up to or beyond 6 months. In the 1st month, a decrease in reflectivity and branching of corneal subbasal nerve fibers was remarkable. In addition, keratocyte activation was seen in the 1st week and lasted up to a month or even later in some cases.

As far our knowledge, there is no study showing the IVCM findings in cornea after ASP, which is a practical and cost-effective treatment option in the rehabilitation of paracentral or peripherally located RCEs.

The cornea epithelium is supplied by a dense subbasal nerve network and DCs (16). These sensory nerve endings and DC processes secrete growth or neurotrophic factors and cytokines to enrich and strengthen the surrounding cells and media. It has been shown that various trophic factors released by corneal nerves regulate corneal wound healing, maintenance of epithelial integrity and as a result corneal transparency as well (15,17). The relation between corneal nerve alterations and corneal diseases such as keratoconus, dry eye disease, neurotrophic keratitis, and infectious keratitis or corneal dystrophies has been demonstrated by IVCM and summarized in a large review by Cruzat et al. (15) The IVCM also used to image the increased density in epithelial DCs which are referred as antigen presenting cells and other inflammatory cells in patients (18,19). In addition, corneal regeneration and wound healing following corneal refractive

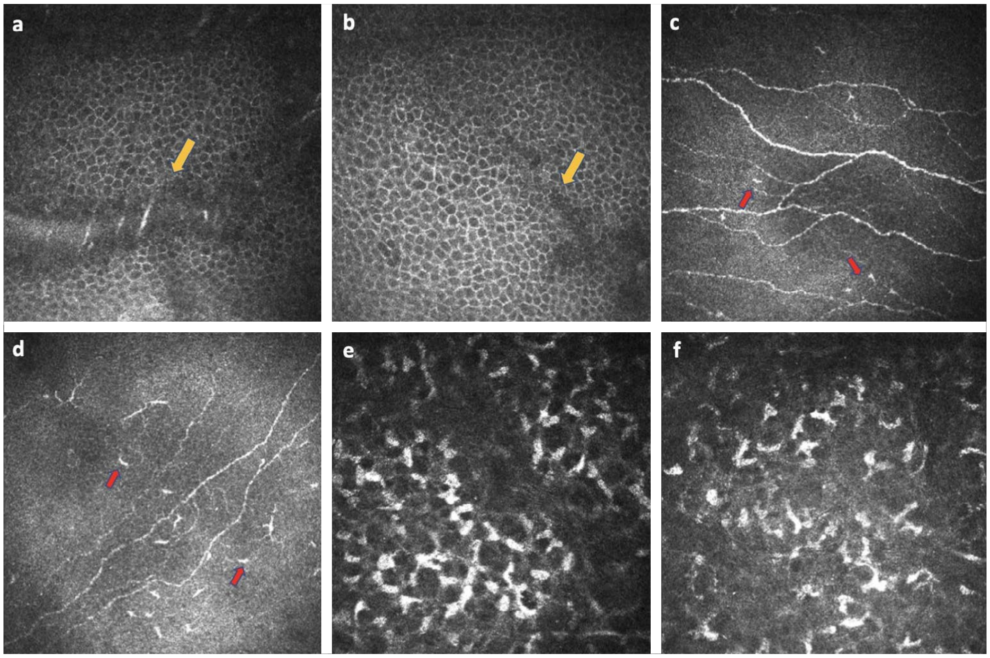

Figure 5. *In vivo* confocal microscopy images at 6th months after anterior stromal puncture. **(a and b)** The epithelium was found to be healed with the scar formation left by the puncture (yellow arrows). A mild-to-moderate number of dendritic cells (red arrows) were visible at the level of subbasal nerve plexus in the images of a patient with **(c)** map-dot-fingerprint dystrophy and a different patient with **(d)** prior corneal trauma. **(e and f)** The stroma seemed to be improved in those patients, respectively.

surgery were investigated in various studies using IVCM (20-23). In vitro studies investigating the inflammatory pathways and wound healing showed a positive correlation between DCs infiltration and significant elevation of cytokine levels (24,25). Hence, these IVCM findings exhibited after ASP may show that ASP might have triggered a wound healing cascade including variable cytokines and growth factors mediated by DCs, subbasal nerve plexus, and activated keratocytes.

Formerly, ultrastructural changes were also documented by electron microscopy in a rabbit model with RCE treated with ASP (12). The authors have stated that corneal incisions began to fill with epithelial cells from the 1st day and activated keratocytes were seen nearby the basement membrane defect on the 7th day and finally, the healing of the basement membrane was completed within 2–4 weeks. At the 5th-month post-procedure, it was reported that the basement membrane was anatomically intact, and the epithelial projections were also persisted showing extension into the stromal incisions. Those findings may also help to explain the existence of prolonged and attack-free period after ASP.

ASP enables the therapy to be individualized and is advised for RCEs located outer the visual axis (10) since it generates subepithelial scars. Because in this procedure, Bowman's layer is penetrated and this intervention leads the loose cornea epithelium to adhere tightly to the subjacent basement membrane, this may cause haze and glare accompanying decrease in visual performance (26,27). There have been a limited number of studies in the literature investigating ASP in the treatment of RCEs and studies pointed out similar results. In a retrospective, consecutive series of RCEs who had underwent ASP, the patients' clinical features and the outcomes of the procedure were investigated (5). The authors reported that the mean age was 37 years and 60% of patients were male. In all, 83.3% of patients had unilateral involvement and trauma was the most common (62.9%) cause in etiology. Finally, 62.9% of 35 eyes were reported as asymptomatic after ASP at the end of 14 months of follow-up. However, 17% of eyes required additional treatment: 16.6% superficial keratectomy, 66% ASP, and 16.7% PTK. In our study, similar results were found in terms of age (mean age 41.5 years), laterality (65.2% unilateral involvement), and attack-free period. The ratio of our relieved patients was found 69.5% at 21-month follow-up. Conversely, most of our patients were female (63.2%) and 30.4% of eyes required additional treatment; 57.1% second ASP, 42.8% third ASP. These results were interpreted that the higher percentage of additional treatment might be due to the longer follow-up period. Because in accordance with the natural course of this disease, as time passes, the probability of developing recurrences may also increase. In addition, the presence of high percentage of eyes with bilateral EBMD should also be considered. As known, bilateral EBMD cases are more diffuse and severe and have differences in pathogenesis from the ones with unilateral localized superficial trauma and it was suggested that the eyes with bilateral EBMD may turn to account better from superficial keratectomy (5). Certainly, further studies are required to find which additional mechanisms play a role in successful ASP treatment.

Our results were also comparable in another large series including 364 episodes of 261 patients which was reported by Reeves et al. (6) In their study, the average age was 46 years, and most of the patients (61%) were female. They reported that the most common cause was trauma (51.3%), while the second most common cause was EBMD (29.1%) in etiology. Similar to our study, it was reported that the mean age was 41.5 years, 63.2% of patients were female, and trauma was the most common reason in etiology (56.5%). Furthermore, they found that a total of 30.5% of the cases recurred and required additional treatment. In the light of their findings, Reeves et al. (6) had concluded that RCE was commonly connected with trauma, female predominance and the one-quarter of surgically treated cases (23.9% for ASP and 26.7% for PTK) had recurred.

Our study had a few limitations. The number of included eyes and patients was limited. An additional control group could have been established. Although all patients had undergone their last confocal scanning at the 6th month of follow-up and it would have been better if we have had designed a longer follow-up and repeated the scan at the 1st year. Moreover, finally, digital quantitative evaluation could have been used in the analysis of corneal DC and subbasal nerve fiber density.

Conclusion

IVCM findings of our study indicate that a wound healing cascade involving corneal DCs and subbasal nerve plexus may play an important role in the mechanism of how ASP works in the treatment of RCE. In addition, as IVCM has the superiority in cross-sectional imaging at cellular level in investigating cornea after surgical procedures, the images may help the surgeon to better understand the post-healing processes and predict the recurrences. Undoubtedly, controlled studies including higher number of patients are needed to further elucidate the mechanism of ASP in the treatment of RCE.

Disclosures

Ethics Committee Approval: The study was approved by the institutional review board (IRB) of Koç University Committee on Human Research (No: 2021.320.IRB1.146) in the light of the tenets of the declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.S., O.M.; Design – M.Z.K., O.M.; Supervision – A.S., O.M.; Research – M.Z.K., A.S., O.M.; Materials – A.S., O.M.; Data collection and/or processing – M.Z.K., A.S., O.M.; Analysis and/or interpretation – M.Z.K.; Literature search – M.Z.K.; Writing – M.Z.K.; Critical review – A.S., O.M.

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