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Original Article

Combined Phototherapeutic Keratectomy and Peripheral Anterior Stromal Puncture for the Treatment of Recurrent Corneal Erosion Syndrome

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Purpose: To investigate the efficacy of the combined phototherapeutic keratectomy (PTK) and peripheral anterior stromal puncture (ASP) compared with that of PTK alone in patients with recurrent corneal erosion syndrome (RCES).

Methods: The medical records of 25 patients (25 eyes) who underwent combined treatment of PTK and peripheral ASP for RCES from March 2016 to May 2017 were retrospectively reviewed. Twenty-three patients (23 eyes) treated with PTK alone from March 2015 to February 2016 served as a control group. All surgeries were performed by a single surgeon. This retrospective clinical study comprised 48 patients (48 eyes) who were followed up for more than 18 months. Clinical records of age, sex, laterality, etiology of RCES, and history of recurrence after treatment were evaluated.

Results: Twenty-five eyes were treated with combined PTK and ASP, and 23 eyes were treated with PTK only. The mean follow-up period was 19.63 ± 2.97 and 19.75 ± 6.83 months, respectively. There were no differences in baseline parameters between the groups. In the combined treatment group, one patient experienced recurrence 6 months after the surgery. In the single treatment group, five patients showed recurrence at 4, 7, 8, 11, and 13 months after the surgery, respectively. Compared to the single treatment group, the combined treatment group showed significantly lower recurrence rate ($p < 0.05$). All recurred patients required no additional treatment except temporary therapeutic contact lenses and topical lubricants.

Conclusions: Our findings suggest that combined treatment of PTK and peripheral ASP is effective in alleviation of symptoms and prevention of recurrence in refractory RCES compared with treatment using PTK alone.

Key Words: Cornea, Keratectomy, Laser corneal surgery, Punctures, Recurrence

Recurrent corneal erosion syndrome (RCES) is a disorder of the epithelial basement membrane (EBM) that is frequently related to a previous history of corneal trauma injury to the superficial cornea [1]. It is characterized by repeated occurrences of corneal epithelium breakdown. Patients experience sudden eye pain usually upon awakening, recurrent episodes of pain, photophobia, tearing, and redness [2]. These symptoms may occur following corneal trauma, may be related to anterior basement membrane dystrophy (ABMD), or may occur spontaneously [3].

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There are many conservative treatment options available for RCES. These options include topical lubricating drops, ointments, warm compresses, punctal plugs, topical steroids, bloodserum drops, hyperosmotic agents, and patching [4]. Despite these conservative treatments, approximately 5% of patients continue to experience recurrent episodes of RCES [5]. In refractory cases, surgical treatments, such as epithelial debridement, anterior stromal puncture (ASP), neodymium-doped yttrium-aluminum-garnet laser (Nd: YAG laser) superficial keratectomy using a diamond burr, alcohol delamination, or phototherapeutic keratectomy (PTK), are required [6,7].

For erosions involving the peripheral cornea, ASP is typically recommended. This procedure causes the epithelium to adhere tightly to the underlying basement membrane. Since Bowman's layer is penetrated during the procedure, ASP generates scars. Therefore, this technique is suggested for cases that do not involve the central visual axis as the aim is to prevent iatrogenic vision loss [8,9]. The procedure produces minimal discomfort and can be performed in an outpatient clinic. In a 2014 report of 35 eyes with RCES, 63% of eyes were symptom free following ASP [10]. The other technique uses an Nd: YAG laser to deliver power bursts to the cornea. The advantage of the Nd: YAG laser is that the stromal punctures are shallower, which limits scar development [1]. Tsai et al. [11] reported that 50% (33 eyes) of patients were symptom free after Nd: YAG laser therapy. Alcohol delamination is another promising method that can be recommended when diamond burr polishing or PTK is not available [12,13]. Dua et al. [14] placed a 20% alcohol solution in a 5-mm optical zone marker for 40 seconds to treat refractory RCES. Unlike other treatments, alcohol delamination neither penetrates nor interrupts Bowman's layer and thus has a low rate of inducing corneal haze. However, alcohol delamination also has some disadvantages. Alcohol use carries the risk of toxicity [12,14]. Alcohol delamination should only be performed under direct visualization through a microscope and cannot be completed using the slit-lamp, unlike ASP.

PTK is the most successful single method for RCES [15]. This procedure can typically be performed within a central 8-mm-diameter zone, although the treatment zone size varies depending on type of excimer laser system. We found that some RCES patients who underwent PTK treatment experienced recurrence in the peripheral area that was not accessible via PTK treatment. In addition, when we carried out alcohol delamination before the PTK procedure, we identified several cases where lesions thought to be located only in the central area actually extended to the periphery. Therefore, we devised a combined treatment of PTK and peripheral ASP to reduce the likelihood of recurrence in the peripheral area untreated by PTK (Fig. 1). ASP is an easy and quite successful method; however, it cannot be performed as evenly as PTK over the entire RCES lesion. Because ASP leaves subepithelial scars, it is also not appropriate if the lesion is located on the visual axis [10]. With combined treatment of PTK and peripheral ASP, visual acuity is not worsened because the subepithelial ASP scars are located in the peripheral area.

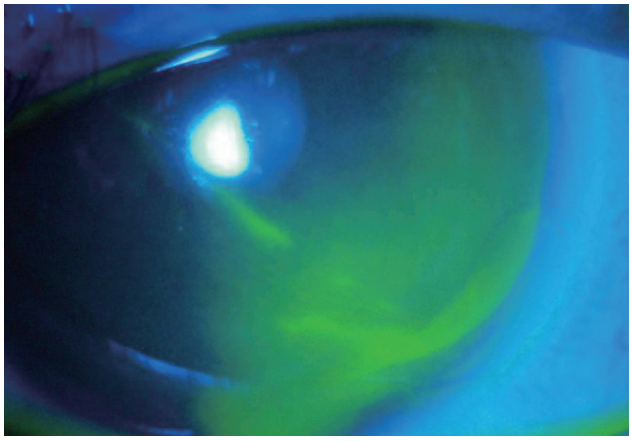

Fig. 1. Clinical photograph (slit-lamp image with fluorescein exciter filter) of a cornea in a patient with recurrent corneal erosions who underwent only phototherapeutic keratectomy treatment seven months ago showing the recurrence in the peripheral area where phototherapeutic keratectomy was not reached.

This report was carried out to compare the effectiveness of combined PTK and peripheral ASP treatment with PTK alone for refractory RCES.

Materials and Methods

This retrospective study was conducted at the Department of Ophthalmology, Kim's Eye Hospital, Konyang University. This study was approved by the institutional review board at Kim's Eye Hospital, Seoul, Korea (A-2015-009). Informed consent was waived due to the retrospective nature of the study.

All procedures of the study followed the guidelines of the Declaration of Helsinki. The medical charts of 48 pa-

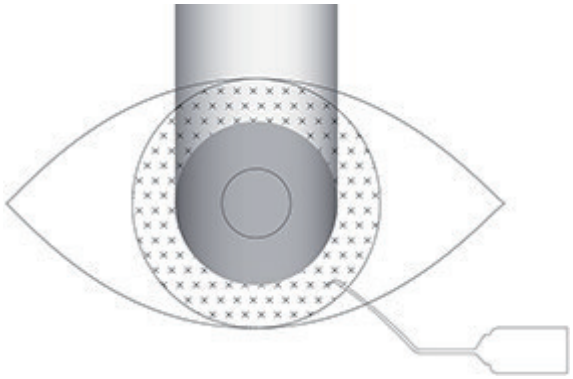

Fig. 2. Schematic diagram of the procedure. After epithelial removal by alcohol application, phototherapeutic keratectomy was performed at central 8-mm zone with 10-μm depth. Thereafter peripheral anterior stromal puncture was made at 360-degree peripheral area outside phototherapeutic keratectomy ablated zone.

tients (48 eyes) were retrospectively reviewed for clinical data of patient age, sex, laterality, flat (K1) and steep (K2) keratometry readings, etiology of RCES, type of treatment for erosive episodes, and history of recurrence after treatment. Reasons for RCES were classified as trauma, ABMD, other etiologies, or unknown. Recurrence was defined as extra episodes of symptomatic RCES that were reported during the follow-up period.

The medical records of 25 patients (25 eyes) who underwent the combined treatment of PTK and peripheral ASP for RCES from March 2016 to May 2017 were reviewed. We compared these results with those of a patient group who underwent treatment with only PTK from March 2015 to February 2016 as the control group. All the surgical interventions were executed by a single expert surgeon. The inclusion criteria were any patient with RCES contained within the visual axis whose symptoms were not cured by conventional treatment and whose follow-up period lasted for more than 18 months. Patients were excluded if they had a history of previous ocular surgery, a history of herpetic eye disease or corneal hypoesthesia, a history of diabetes mellitus, or were younger than 18 years.

Outcome measures involved laterality, demographics, preoperative keratometry value, history of corneal trauma, additional treatments required, and complications.

Briefly, the PTK operation was completed as follows. The eye was anesthetized with one drop of topical 0.5% proparacaine hydrochloride (Alcaine; Alcon Laboratories, Fort Worth, TX, USA), cleansed with povidone iodine, and covered with a sterilized drape. A lid speculum was applied. The surgical procedure is shown in Fig. 2 and in Video 1 in the supplementary file. The corneal surface was dried with a cellulose sponge, and a 9.5-mm alcohol solution holding well (LASEK Alcohol Well, K3-1822; Katena Products, Denville, NJ, USA) was held inflexibly on the central cornea. Next, 50 μL (4–5 drops) of 20% alcohol solution was placed within the well for 20 seconds. After the alcohol application, the ocular surface was copiously rinsed with a balanced salt solution (BSS, Alcon Laboratories) for 15 seconds. The loosened epithelium was removed with a dry cellulose sponge and a LASEK spatula with a semi-circular tip and a beveled edge (LASEK Micro Hoe & Epi Peeler, K3-1848; Katena Products).

A PTK treatment was performed with an 8-mm treatment zone at a depth of 10 μm using an excimer laser system (Wavelight EX500, Alcon Laboratories). The cornea was then washed with chilled BSS for 5 seconds and dried with a cellulose sponge.

The peripheral ASP procedure was added only in the combined treatment group in a 360-degree peripheral area outside of the 8-mm PTK ablated zone. The physician proceeded with a needle holder and the tip of a short (5 / 8 inch) 26- or 30-gauge needle attached to a 1-mL syringe with the bevel up. The needle tip was bent down, and the bent needle hub was up, as is customary with cystotomes in cataract surgery. The physician then held the syringe and aimed the needle tip 90 degrees toward the cornea to indent the affected lesion, creating micropunctures over the area. The punctures were less than 1-mm apart. A schematic diagram of the procedure is shown in Fig. 2. Thereafter, the entire cornea was washed with BSS. After applying a therapeutic lens, the speculum was removed.

Patients were prescribed 0.5% levofloxacin eye drops (Cravit; Santen Pharmaceutical, Osaka, Japan) four times daily, a lubricating gel (Liposic; Bausch and Lomb, Rochester, NY, USA) once daily before sleep, and 0.15% sodium hyaluronate (Hyabak; Thea, Clermont-Ferrand, France) and autologous serum eyedrops four times daily.

The therapeutic lens was exchanged at one- to two-week intervals and removed 1 month postsurgery. Preservative-free 0.15% sodium hyaluronate and lubricating ointment were recommended for at least three months. Preservative-free 0.05% cyclosporine eyedrops (Restasis; Allergan, Irvine, CA, USA) were used after removing the therapeutic lens to prevent dry eye syndrome. Hot compresses and lid scrubs were recommended if the patients

experienced meibomian gland dysfunction.

PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA), was used for statistical analyses. Fisher exact test was used to compare the results between the two treatment groups. A *t*-test and Pearson chi-square test were used to test the difference between the two groups. Kaplan-Meier survival estimates were compared with log-rank tests. A *p*-value <0.05 was considered statistically significant.

Results

Table 1 summarizes the age, sex, etiology, treated side, follow-up period, and incidence of RCES recurrence for each patient in the study. In the combined treatment group, 48% of the patients (12 / 25) were men, and the mean age of patients was 44.24 ± 12.93 years. In the single treatment group, 53% of the patients (12 / 23) were men, and the mean age of the patients was 43.57 ± 13.20 years. In the combined treatment group, 48% of the patients (12 / 25) had right eye involvement, and the mean preoperative K1 of the patients was 42.89 ± 1.79; the mean preoperative K2 of the patients was 43.72 ± 1.88. In the single treatment group, 43% of the patients (10 / 23) had right eye involvement; the mean preoperative K1 of the patients was 42.94 ± 2.28, while the mean preoperative K2 of the patients was 44.04 ± 2.27. In the combined treatment group, 80% of the patients (20 / 25) had a prior history of trauma, and 8% (2 / 25) had ABMD. The mean follow-up period was 19.63 ± 2.97 months. In the single treatment group, 83% of the patients (19 / 23) had a prior history of trauma, and 4% (1 / 23) had ABMD. The mean follow-up period was 19.75 ± 6.83 months. There was no significant difference between the two groups in any of the aforementioned parameters.

Table 1. Comparison of the combined treatment group (group 1) and the single treatment group (group 2)

	Group 1	Group 2	*p*-value
Number of eyes	25	23	NA
Age (yr)	44.24	43.57	0.859*
Sex (female : male)	13 : 12	11 : 12	0.773†
Laterality (right : left)	12 : 13	10 : 13	0.753†
Preoperative K1	42.89	42.94	0.931*
Preoperative K2	43.72	44.04	0.592*
Etiology			1.00‡
History of trauma	20	19	
ABMD	2	1	
Other/unknown	3	3	
Follow-up (mon)	19.63	19.75	0.935*
Recurrences	1 / 25	5 / 23	0.037‡

NA = not applicable; K1 = flat keratometry readings; K2 = steep keratometry readings; ABMD = anterior basement membrane dystrophy.
* *t*-test; †Pearson chi-square test; ‡Log-rank test.

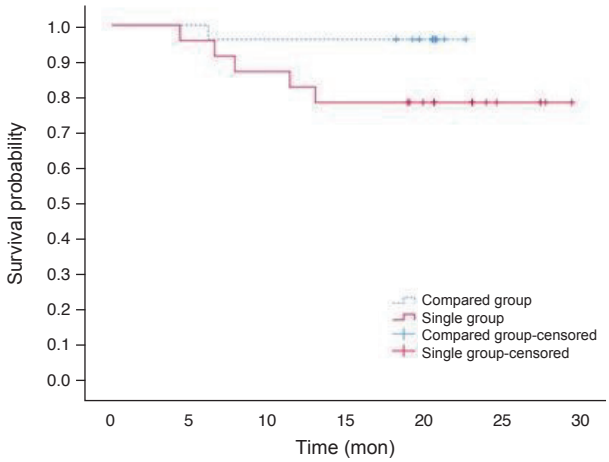

Fig. 3. Kaplan-Meier survival curve demonstrating the time to recurrence of recurrent corneal erosion syndrome symptoms after each treatment. Compared to phototherapeutic keratectomy only treatment group, the combined phototherapeutic keratectomy and peripheral anterior stromal puncture treatment group showed significantly lower recurrence rates (log-rank test, p = 0.037).

In the combined treatment group, one patient experienced a recurrence at six months postoperatively. In the single treatment group, five patients recurred at 4, 7, 8, 11, and 13 months postsurgery, respectively. Of the five cases that recurred in the PTK-only group, two recurred in the central area, while three recurred in the peripheral area. One case of recurrence in the combined group recurred in the central area. The recurrence rate of the combined treatment group was 4% (1 / 25) during the follow-up period. The recurrence rate of the single treatment group was 21% (5 / 23) during the follow-up period. A Kaplan-Meier survival curve demonstrated the time to recurrence of corneal erosion syndrome symptoms after each treatment. Compared to the PTK-only treatment group, the combined PTK and peripheral ASP treatment group showed significantly lower recurrence rate (log-rank test, p = 0.037). According to the Kaplan-Meier method, the likelihood of

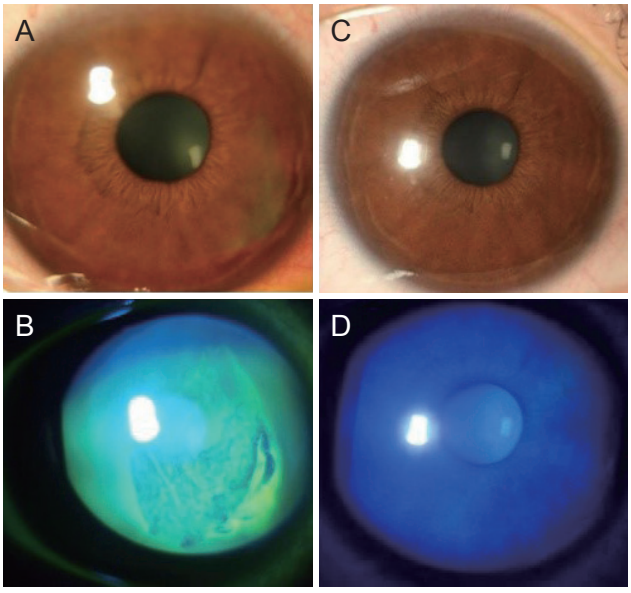

Fig. 4. Clinical photograph of patient treated with the concurrent treatment of phototherapeutic keratectomy and peripheral anterior stromal puncture. (A) Preoperative photograph demonstrating macroform erosion. (B) Fluorescein photograph demonstrating erosion. (C) Clinical appearance 2 months after the operation. (D) Fluorescein photograph 1 week after the operation.

survival rates after each treatment is shown in Fig. 3. If RCES did not recur, the participant was considered a survival case for the sake of the survival analysis.

A clinical photograph of a patient who only underwent PTK and experienced a recurrence in the peripheral area where the PTK could not reach is shown in Fig. 1. Preoperative and postoperative clinical photographs of a patient in the combined treatment group are shown in Fig. 4A-4D. No patient with recurrence was prescribed additional treatments except temporary therapeutic contact lenses and topical lubricants.

Discussion

PTK allows precise removal of corneal tissue at the level of the layer or in the anterior stroma. The nonstandard adhesion of the corneal epithelium in RCES is thought to be associated with abnormal hemidesmosomes, disruption of adhesion by metalloproteinases, and/or duplication of the EBM [14,16]. The goal of surgical treatment is to eradicate the loose epithelium and the basement membrane to allow restoration of a new epithelium and establishment of more productive adhesion complexes [1]. The basis for partial ablation of Bowman's layer in RCES is to reinforce adhesion of the basal epithelial cells to the underlying tissue and to remove debris from the basal membrane [16]. By treating Bowman's layer, a new bed for the migrating epithelium is formed, and the hemidesmosomal adhesion complex is enhanced [17]. Because corneal opacity is usually not caused by a 10-μm ablation depth, and mitomycin-C might inhibit EBM complex regeneration, intraoperative mitomycin-C application is typically not performed [18].

In the combined treatment group, one patient experienced recurrence at six months postoperatively. In the single treatment group, five patients had recurrence at 4, 7, 8, 11, and 13 months post-surgery, respectively. The success rate of the combined treatment group was 96% (24 / 25) during the follow-up period, while the success rate of the single treatment group was 79% (18 / 23) during follow-up. There are many reports on the treatment of RCES with PTK. The reported rate of success regarding alleviation of symptoms and prevention of RCES varies between reports [14]. Baryla et al. [19] reported a recurrence rate of 25% by three months and 36% by nine months after PTK. Likewise, Dedes et al. [5] showed 72% of 85 eyes to be symptom-free eyes after PTK. It has been reported that recurrences after PTK usually occur between 3 and 10 months postoperatively [19]. In the present study, the symptoms recurred in six total eyes between postoperative month 4 and postoperative month 13, a relatively short period after surgical treatment.

The maximal PTK treatment zone size of various excimer laser systems is as follows: 8 mm (Wavelight EX500; Alcon Laboratories), 6.5 mm (VISX S4; VISX Inc., Santa Clara, CA, USA), 7 mm (Technolas Teneo 317; Bausch & Lomb Technolas Perfect Vision GmbH, Dornach, Germany), 8 mm (MEL 90; Carl Zeiss Meditec AG, Jena, Germany), and 12 mm (Schwind Amaris; SCHWIND eye-tech-solutions GmbH, Kleinostheim, Germany) [20-23]. Other than the Schwind Amaris model, the majority of currently available excimer laser systems allows for a PTK treatment zone smaller than 8 mm. Therefore, there is potential for recurrence of RCES outside the PTK-treated zone (Fig. 1). The area of epithelial loosening after alcohol application is usually larger than the size of the original RCES lesion observed by slit-lamp examination with fluorescent dye staining. These areas may be potential sources of recurrence; therefore, the ASP was performed more intensively

in these areas, often even extending to the PTK-ablated area. By performing additional peripheral ASP, scar tissue is created between the anterior stroma and the corneal epithelium, which improves epithelial adherence. This concept is similar to the use of peripheral 360-degree barrier lasers in retinal treatments.

Instead of peripheral ASP, a series of small (3–4 mm diameter) PTK spots can be performed peripherally [24]. The excimer laser system usually has an automatic eye tracker system that improves surgical precision [25,26] and ensures that the eye maintains the correct position. However, the eye tracker function should not be used when performing a peripheral PTK procedure; it should be manually operated instead. Performing at least 10 peripheral small-size PTKs without the eye tracker is very time-consuming, and it is difficult to locate each PTK area. Furthermore, if the patient moves the eye, the lasers might be extended over the corneal limbus and may overlap with a pre-ablated area. This movement may also result in an uneven corneal surface and an irregular astigmatism.

In this study, we compared the efficacy of combined PTK and peripheral ASP with PTK alone for treatment of RCES. The combined treatment of PTK and peripheral ASP offers a quick and comfortable alternative for patients with RCES. PTK is an effective treatment for RCES, but there have been recurrences in the peripheral areas the PTK could not reach. PTK leaves no visible spots or scars, and peripheral ASP reduces recurrence of RCES in the peripheral area. The combined PTK and peripheral ASP treatment lowered the recurrence rates in the peripheral areas that the PTK could not access.

The major limitations of this research were the small number of patients and the limited follow-up period. A larger, randomized, controlled, clinical trial comparing combined PTK and peripheral ASP treatment with PTK alone is essential to confirm these results.

In conclusion, combined PTK and peripheral ASP is effective in alleviation of symptoms and prevention of recurrence in RCES refractory to conservative measures.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

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