

Efficacy and Safety of Secondary Surgical Treatment for Refractory Recurrent Corneal Erosion

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Purpose: To investigate the efficacy and safety of secondary surgical intervention of combined phototherapeutic keratectomy (PTK) with alcohol delamination and peripheral anterior stromal puncture (ASP) for refractory recurrent corneal erosion (RCE).

Methods: This retrospective comparative study defined refractory RCE as cases persisting for more than 6 months after primary surgical intervention. A total of 115 eyes from 115 patients with refractory RCE, treated either with (n = 92) or without (n = 23) the secondary surgical treatment combining PTK and ASP between January 2021 and January 2023, were included. The Kaplan–Meier survival analysis method was used to determine the intervention's efficacy.

Results: The mean age was 34.4 ± 10.8 years, with a predominance of male patients (60%). Over a follow-up period exceeding 1 year, the recurrence rate was markedly lower at 27.2% in the group undergoing secondary surgical treatment compared with 69.6% in those receiving conservative treatment. Kaplan–Meier survival analysis revealed significantly reduced recurrence rates in the surgical group versus the conservative treatment group (log-rank test, $P = 0.007$). Notably, 96% of recurrences in the surgical cohort occurred within the first 6 months postintervention, with no recurrences observed after 9 months. At the final follow-up, 12% necessitated further surgical procedures 6 months after the secondary intervention. The study reported no significant surgical complications.

Conclusions: The secondary surgical approach combining PTK with alcohol delamination and ASP presents a viable and safe treatment alternative for patients with refractory RCE, demonstrating a significant reduction in recurrence rates.

Key Words: alcohol delamination, anterior stromal puncture, phototherapeutic keratectomy, recurrent corneal erosion

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Recurrent corneal erosion (RCE) is a common disease of the epithelial basement membrane of the cornea, leading to repeated episodes of eye pain, blurred vision, tearing, and photophobia, typically on awakening.^{1,2} This condition primarily results from mechanical injuries (accounting for 45%–64% of cases) or a disorder known as epithelial basement membrane dystrophy (19%–29%).^{1,3} The issue arises when the cornea's epithelial layer fails to securely attach to the underlying basement membrane because of its abnormal basal lamina, making it prone to detachment upon mechanical stress such as dry eye condition.

Treatment for RCE is categorized into acute and long-term phases.⁴ Initially, the focus is on healing the damaged corneal surface. After that, prophylactic treatments are recommended for 6 to 12 months continuously to enhance ocular surface lubrication, thereby reducing mechanical stress, and to regulate inflammatory modulators such as metalloproteinase-9 to strengthen epithelial adhesion.^{3,5–7} Medical approaches can be tried initially.^{1,8} Previous studies have shown that 25% of patients had a relapse when wearing therapeutic bandage contact lens alone every 2 weeks for 3 months.² The combined use of hypertonic saline drops and overnight ointment for 6 to 12 months resulted in a recurrence rate of approximately 15%.⁹

For cases unresponsive to conservative treatments, surgical options such as anterior stromal puncture (ASP), diamond burr polishing, Nd:YAG laser stromal puncture, and phototherapeutic keratectomy (PTK) are considered, with success rates varying by technique but generally exceeding 60% to 80%.^{10–13}

Despite the availability of these treatments, there remains a gap in knowledge regarding the management of refractory RCE that fails these treatment modalities. Previous studies have provided limited information on the management of patients who experience a recurrence after surgery for RCE. This research assesses the efficacy and safety of a secondary surgical intervention that combines PTK with alcohol delamination and ASP, in treating patients who have not seen improvement after surgical treatment for over 6 months.

MATERIALS AND METHODS

This retrospective comparative study was conducted at Eyejun Ophthalmic Clinic. The study was reviewed and

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approved by the Institutional Review Board of the Public Institutional Bioethics Committee (IRB approval number: P01-202311-01-009), adhering to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

Subjects

The study enrolled consecutive patients who were diagnosed with refractory RCE between January 2021 and January 2023. All participants were followed for a minimum duration of 1 year. Refractory RCE was identified based on the following criteria: 1) the presence of a persistent epithelial loosening on slit-lamp examination in the central to mid-peripheral cornea attributed to RCE; 2) a history of prior surgical interventions including ASP, diamond burr polishing, Nd:YAG laser stromal puncture, and PTK; and 3) an unsuccessful outcome from at least 6 months of medical and conservative treatment aimed at RCE resolution. To evaluate the efficacy and safety of the secondary surgical intervention, the study also included patients with refractory RCE who declined the secondary surgery. In instances where participants presented with refractory RCE in both eyes, a single eye was selected for the study's focus through a random number generator program, ensuring an unbiased selection process and enhancing the study's methodological rigor.

Surgical Technique

The secondary surgical intervention comprised a sequenced procedure integrating alcohol delamination, PTK, and peripheral ASP, using the excimer laser platform (Amaris1050RS, Schwind eye-tech-solutions GmbH, Kleinostheim, Germany).^{14,15} The initial step involved the application of 0.5% proparacaine hydrochloride (Alcaine; Alcon Laboratories, Fort Worth, TX) to anesthetize the eye, followed by sterilization with povidone iodine and the placement of a sterile drape. A lid speculum was inserted to maintain eyelid separation. The corneal surface preparation began with dehydration using a cellulose sponge. This was followed by the positioning of a 9.5-mm alcohol solution holding well centrally on the cornea, into which a 20% alcohol solution diluted with sterile water was instilled for 20 seconds to loosen the epithelium. After alcohol exposure, the ocular surface underwent a 15-second rinse with balanced salt solution. The loosened epithelial layer was then delicately removed employing a dry cellulose sponge and a LASEK spatula specifically designed for the task. PTK was executed over a 9-mm zone to a precise depth of 5 μm using the excimer laser.¹⁶ Mitomycin C was not used. After PTK, the cornea was irrigated with chilled balanced salt solution for 5 seconds and dried. The ASP technique was applied to the periphery outside of 6.5 mm on the laser platform with a ruler from the light guide point of the platform, where micro-punctures were made using a specially curved 30G needle to ensure consistent depth (5/8 inch) and spacing (<1 mm apart). A therapeutic contact lens (Acuvue Oasis therapeutic bi-weekly contact lens; Johnson & Johnson, Jacksonville, FL) was applied, with plans for replacement every 1 to 2 weeks,

scheduled for removal 1-month postsurgery. Postoperatively, patients were prescribed 0.5% levofloxacin eye drops (Cravit; Santen Pharmaceutical, Osaka, Japan), to be used 4 times daily, and a nightly regimen of lubricating gel (Liposic; Bausch and Lomb, Rochester, NY). Topical steroid was not used after the procedure. The conservative regimen also included the use of preservative-free 0.15% sodium hyaluronate eye drops and a lubricating ointment, recommended for at least 6 months after the surgery.

Statistical Analysis

To assess the effectiveness of the secondary surgical treatment, the Kaplan-Meier survival analysis was used. In addition, Mann-Whitney test and χ^2 test were applied to examine epidemiological differences and recurrence rates between the 2 groups under study. A *P*-value of <0.05 was deemed to indicate statistical significance.

RESULTS

The investigation encompassed 115 eyes from an equal number of patients. Within this cohort, 92 patients underwent the secondary surgical, whereas the remaining 23 received conservative management (Table 1). Comparative analysis of the 2 groups revealed no statistically significant differences regarding age, sex, laterality, etiology, primary surgical procedure, period prevalence of RCE, number of recurrences before observation, and follow-up duration.

The investigation revealed a pronounced disparity in recurrence rates between the intervention cohorts, with the group undergoing secondary surgical treatment exhibiting a 27.2% recurrence rate, significantly lower than the 69.6% observed in the conservative management group (*P* <0.001). Kaplan-Meier survival analysis provided further insight into the temporal dynamics of treatment efficacy. One month after treatment, the survival probability—indicative of the absence of recurrence—stood at 90.9%. This figure gradually diminished over time, registering at 74.8%, 66.1%, and 60.6% after 3, 6, and 12 months, respectively (Fig. 1). The survival analysis underscored a significantly enhanced probability of survival, free from recurrence, within the secondary surgical treatment group across the study duration when contrasted with the conservative treatment cohort (log-rank test, *P* = 0.007).

Notably, 96% of recurrences in the secondary surgical treatment group occurred within the first 6 months after treatment, and no recurrences were reported after 9 months of combined treatment. At final follow-up, 88.0% of patients who experienced recurrence after the secondary intervention successfully managed their condition through medical therapy and conservative approaches alone. Conversely, 12% of patients necessitated an additional surgical procedure (ASP alone) 6 months after the initial secondary surgery.

Throughout the follow-up duration, the cohort undergoing surgical intervention reported certain complications. Specifically, 13% of patients experienced blurred vision, and 8.7% developed corneal opacity along the visual axis

TABLE 1. Demographics and Characteristics of Study Subjects

	Second Surgical Intervention (n = 92)	Conservative Treatment Alone (n = 23)	P
Age (yr, mean \pm SD)	35.1 \pm 11.5	31.3 \pm 7.1	0.281
Sex (n (%)) of male)	55 (59.8)	14 (60.9)	0.924
Laterality (n (%)) of right)	45 (48.9)	8 (34.8)	0.224
Etiology (n, %)			0.948
Trauma	45 (49.0)	12 (52.2)	
Epithelial basement membrane dystrophy	27 (29.3)	6 (26.1)	
Others/unknown	20 (21.7)	5 (21.7)	
Primary surgical procedure (n, %)			0.707
ASP	60 (65.2)	14 (61.0)	
Diamond burr polishing	2 (2.2)	1 (4.3)	
Nd:YAG laser stromal puncture	6 (6.5)	1 (4.3)	
PTK	25 (27.2)	7 (30.4)	
Dry eye assessments†			
NIKBUT-1 (s)	6.5 \pm 4.9	5.3 \pm 3.0	0.265
Presence of aqueous deficiency (no. of patients, %)	55 (53.6)	12 (13.4)	0.508
MGD grade	1.8 \pm 1.2	2.1 \pm 1.0	0.134
Period prevalence (mo, mean \pm SD)	20.6 \pm 10.7	23.0 \pm 9.0	0.333
No. of recurrences before observation (n, mean \pm SD)	13.6 \pm 20.0	9.5 \pm 13.7	0.198
Follow-up duration (mo, mean \pm SD)	14.1 \pm 3.2	13.5 \pm 4.6	0.366
Recurrence (no. of patients, %)	25 (27.2)	16 (69.6)	<0.001*

MGD, meibomian gland dysfunction; TMH, tear meniscus height.

*P < 0.001.

†Dry eye was assessed by NIKBUT-1, presence of aqueous deficiency, MGD grade. Keratograph 5M was used to measure NIKBUT-1, TMH. TMH <200 μ m was considered as aqueous deficiency. MGD grade was based on the criteria presented at the 2011 international workshop on meibomian gland dysfunction.

with visual disturbance at 1 month after the procedure. The complications decrease progressively over time, with the highest percentage observed in the first month (approximately 17.4% of patients) and no patients reporting significant side effects caused by the intervention beyond the sixth month (Fig. 2). Furthermore, the study recorded no instances of corneal perforation, infection, or significant refractive shifts, including hyperopic changes exceeding 0.50 diopters.

DISCUSSION

Our study highlights the efficacy of a combined secondary surgical treatment—PTK and ASP—in managing refractory RCE. The observed recurrence rate of approximately 27% over a 1-year follow-up contrasts markedly with the nearly 70% recurrence rate in patients managed solely with medical and conservative treatments. Most recurrences after secondary surgical treatment in our study (22 out of 25 cases) were effectively managed with ongoing medical

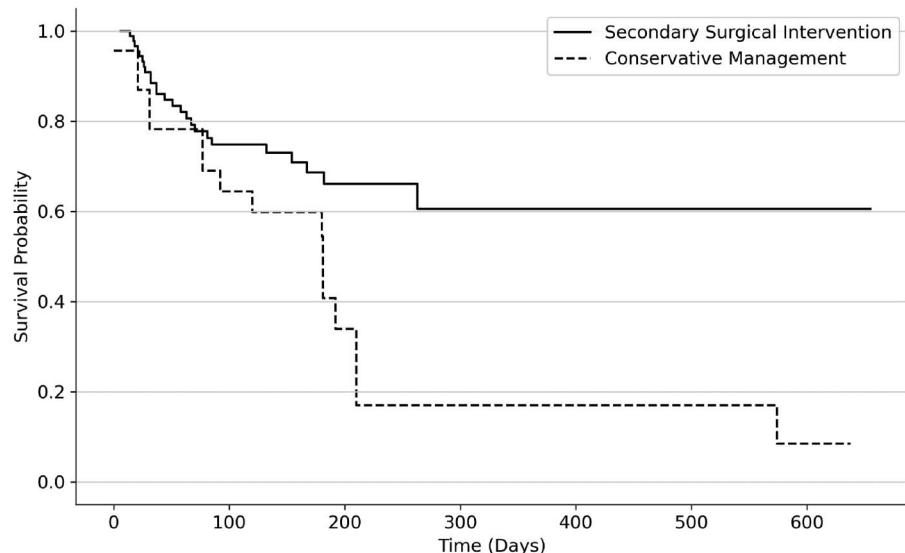


FIGURE 1. Kaplan-Meier curves for secondary surgical intervention and conservative management. The survival analysis underscored a significantly enhanced probability of survival, free from recurrence, within the secondary surgical treatment group across the study duration when contrasted with the conservative treatment cohort (log-rank test, P = 0.007).

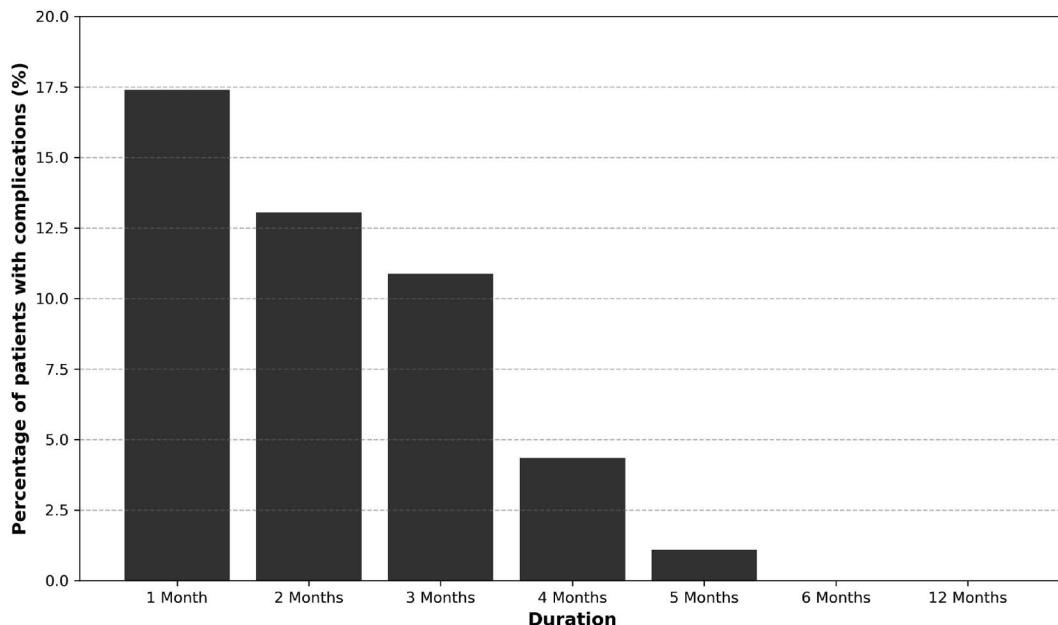


FIGURE 2. Percentage of patients with complications after secondary surgery over a year period. The graph illustrates a decline in the incidence of complications over time, with the highest prevalence (approximately 17.4%) occurring during the initial month. It is noteworthy that no patients reported complications beyond the sixth month.

therapy, with only 3 cases necessitating an additional ASP procedure. This significant difference underscores the potential of a secondary surgical intervention in cases where RCE persists despite initial surgical and conservative management efforts.

The pathophysiology behind RCE involves prolonged or repeated epithelial defects, which may lead to structural changes in the corneal tissue, including scarring, thereby complicating the healing process.¹⁷ Considering the altered corneal state in refractory cases, the efficacy of a secondary procedure was anticipated to differ from initial interventions. Our findings affirm the viability of this approach, even in the context of treating advanced or complicated RCE cases.

Mechanistically, ASP and PTK enhance epithelial adhesion by promoting the development of junctional complexes, such as hemidesmosomes and anchoring fibrils, crucial for cellular attachment.^{10,18} PTK, in particular, is known for creating a smooth epithelial bed that facilitates reduced recurrence rates, possibly because of the microscopic roughness allowing for better epithelial adherence.¹⁹

The extent of the PTK effect can vary with the level of ablation and can extend from Bowman layer to the anterior stroma, areas often compromised by structural irregularities.²⁰ In a previous study, patients with recurrence after 8-μm depth PTK were treated with an additional 8-μm depth PTK with no recurrence.²¹ The authors speculated that recurrence occurred because a smooth epithelial bed could not be formed sufficiently for epithelial adhesion with the first 8-μm depth PTK and improved with further treatment. In this study, an excimer laser treatment with a depth of 5 μm was used. Although the depth of the epithelial bed was not directly assessed, considering the long-term recurrent episodes expe-

rienced by the subjects, it is advisable to conduct further research to explore whether adjusting the ablation depth on an individual basis could lead to a lower recurrence rate.

The principal limitation of this study is its retrospective, nonrandomized design, which precludes the isolation of the effects of the combined treatment from those associated with underlying conditions or prior surgical interventions and managements. Further research should concentrate on unravelling the complex web of factors that contribute to refractory RCE and evaluating the specific outcomes of secondary surgical treatments. Although the complications observed after secondary surgery in this study were transient and did not result in significant clinical issues, the potential impact on patients' quality of life because of reduced vision cannot be entirely ruled out. The combined approach of alcohol delamination, PTK, and ASP was implemented under the assumption that the initial surgical intervention may have been insufficient to address the patient's condition. However, it is essential to exercise caution to avoid overtreatment, ensuring that therapeutic decisions are tailored to the individual needs of each patient.

In conclusion, the combined application of PTK and peripheral ASP presents a promising and safe treatment modality for patients with refractory RCE who have not responded to initial surgical and conservative management. This study advocates for the consideration of a secondary surgical strategy in patients who remain symptomatic despite exhaustive conservative and primary surgical interventions. To further substantiate these findings, prospective studies are necessary to confirm the efficacy of the combined treatment and to evaluate the long-term outcomes, ensuring a more robust understanding of its benefits and potential risks.

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