ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/ophthal.2025-109226

Topical Cyclosporine A 0.05% as a Minimally Invasive Alternative to Punctoplasty for Severe Acquired Punctal Stenosis: A Prospective Interventional Study

Şiddetli Edinsel Punktum Stenozunda Punktoplastiye Alternatif Olarak Minimal İnvaziv Bir Seçenek: Topikal Siklosporin A %0.05: Prospektif Girişimsel Çalışma

Murat OKLAR[a], Titap YAZICIOĞLU[a], Anıl AĞAÇKESEN[a], Gizem KARDAŞ[a], Raziye DÖNMEZ GÜN[a]

[a]University of Health Sciences Faculty of Medicine, Kartal Dr. Lütfi Kırdar City Hospital, Department of Ophthalmology, İstanbul, Türkiye

ABSTRACT Objective: To assess the therapeutic effectiveness of cyclosporine A 0.05% ophthalmic solution in treating grade 1 acquired punctal stenosis and compare its outcomes with rectangular 3-snip punctoplasty. **Material and Methods:** This prospective study included 33 patients with fibrotic or membranous grade 1 punctal stenosis. Punctal dilation, canalicular probing, and nasolacrimal duct irrigation were performed on all patients before being assigned to Group A (n=17, cyclosporine A %0.05 eye drops twice daily for 6 months) or Group B (n=16, punctoplasty). Epiphora was assessed using the Fluorescein Dye Disappearance Test (FDDT), Munk score, and Lac-Q questionnaire at baseline, 6 weeks, and 6 months. Functional success was defined as a Munk score of 0-1 and an FDDT grade of 0-2, while anatomical success was determined by the presence of a grade 3 punctum at the 6-month follow-up. **Results:** Both groups showed significant improvement in Munk, Lac-Q, and FDDT scores over time (p<0.001). At 6 months, Group A had significantly lower Munk scores (p=0.004) and better FDDT scores at 6 weeks (p=0.002) than Group B. Functional success was greater in Group A (76.5%) compared to Group B (43.8%) (p=0.052, odds ratio=4.18). Punctal restenosis occurred in 21.2% (7/33), all with fibrotic-type stenosis. **Conclusion:** Cyclosporine A demonstrated greater functional success than punctoplasty despite similar anatomical outcomes, suggesting inflammatory modulation as a key factor in treatment. Given the persistence of functional epiphora and restenosis risk after punctoplasty, cyclosporine A may be a promising alternative. Additional large-scale studies are required to evaluate its long-term effectiveness.

Keywords: Lacrimal apparatus diseases; cyclosporine

ÖZET Amaç: Topikal siklosporin A 0.05% göz damlasının grade 1 edinsel punktum stenozu tedavisindeki etkinliğini değerlendirmek ve sonuçlarını rektangular "3-snip" punktoplasti ile karşılaştırmak. **Gereç ve Yöntemler:** Bu prospektif çalışmaya fibrotik veya membranöz grade 1 punktum stenozu tanısı almış 33 hasta dâhil edildi. Tüm hastalara punktum dilatasyonu, Kanaliküler açıklığın prob ile değerlendirilmesi ve nazolakrimal kanal irrigasyonu yapıldıktan sonra 2 gruba ayrıldı: Grup A (n=17, hastalara günde 2 kez olacak şekilde 6 ay boyunca siklosporin A %0.05 göz damlası) ve Grup B (n=16, punktoplasti). Hastaların epiforası Floresein Boya Kaybolma Testi (FDDT), Munk skoru ve Lac-Q anketi ile başlangıçta, 6. haftada ve 6. ayda değerlendirildi. Fonksiyonel başarı, Munk skoru 0-1 ve FDDT skoru 0-2 olarak tanımlandı, anatomik başarı ise 6. ayda grade 3 punktum elde edilmesi olarak kabul edildi. **Bulgular:** Her iki grupta Munk, Lac-Q ve FDDT skorlarında anlamlı iyileşme gözlendi (p<0,001). 6. ayda, Grup A'nın Munk skorları anlamlı derecede daha düşük bulundu (p=0,004) ve 6. haftada FDDT skorları Grup B'ye kıyasla daha iyiydi (p=0,002). Fonksiyonel başarı Grup A'da %76,5, Grup B'de %43,8 olarak hesaplandı (p=0,052, odds ratio=4,18, 95% güven aralığı: 0,94-18,61). Punktal restenoz %21,2 oranında (7/33) gözlendi ve tümü fibrotik tip stenozu olan hastalarda gelişti. **Sonuç:** Siklosporin A göz damlası, anatomik sonuçlar benzer olmasına rağmen punktoplastiye kıyasla daha yüksek fonksiyonel başarı göstermiş ve enflamasyonun edinsel punktum stenozu yönetiminde önemli bir rol oynadığını düşündürmüştür. Punktoplasti sonrası fonksiyonel epiforanın devam edebilmesi ve restenoz riski göz önünde bulundurulduğunda, siklosporin A gibi minimal invaziv alternatifler ümit verici bir tedavi seçeneği olabilir. Uzun dönem sonuçlarını değerlendirmek için geniş ölçekli çalışmalar gerekmektedir

Anahtar Kelimeler: Lakrimal sistem hastalıkları; siklosporin

Correspondence: Murat OKLAR
University of Health Sciences Faculty of Medicine, Kartal Dr. Lütfi Kırdar City Hospital, Department of Ophthalmology, İstanbul, Türkiye
E-mail: drmuratoklar@gmail.com

Peer review under responsibility of Turkiye Klinikleri Journal of Ophthalmology.

Received: 06 Feb 2025 ***Received in revised form:*** 23 May 2025 ***Accepted:*** 23 May 2025 ***Available online:*** 14 Jul 2025

Punctal stenosis is a prevalent cause of epiphora, often occurring alongside canalicular or nasolacrimal duct obstruction. It may be present from birth or acquired later due to factors such as ocular inflammation or infection, drug toxicity, eyelid malposition, trauma, tumors, or age-related changes. Various harmful stimuli can trigger chronic inflammation, ultimately leading to fibrosis as a key ultrastructural response. In some cases, concurrent involvement of the canaliculi, nasolacrimal sac, or duct may contribute to the condition.[1-4]

Management of pure punctal stenosis generally involves punctal dilation, surgical correction through punctoplasty, or the use of canalicular tubes or punctal plugs for stenting.[5-7] However, in severe cases, intubation or punctal plug placement may not always be feasible, and premature tube loss can occur. An alternative surgical approach, conjunctivodacryocystorhinostomy with permanent tube implantation, offers another option, though its outcomes vary significantly. Complications such as tube occlusion, dislocation, and conjunctival granuloma formation may arise, and the long-term efficacy of this procedure remains uncertain.[8,9] Moreover, in Türkiye, the high cost of the tube, which is not reimbursed, imposes a financial burden, restricting its widespread use.

Nassief et al. conducted a study showing the efficacy of cyclosporine A in treating epiphora linked to acquired punctal stenosis, which is primarily driven by inflammatory mechanisms.[10] In our study, by incorporating surgical papilla creation when necessary, we aimed to evaluate medical and surgical treatment approaches by comparing the clinical outcomes of ophthalmic solution, applied to reduce the risk of restenosis following punctal dilation and probing, with the 3-snip punctoplasty procedure. Our focus is on patients with severe acquired punctal stenosis, classified as fibrotic or membranous grade 1.

MATERIAL AND METHODS

This prospective interventional study involved 33 patients with grade 1 severe punctal stenosis, presenting with excessive tearing and a symptom duration of at least 6 months. These patients were referred to the Oculoplasty Section of the Ophthalmology Department at Kartal Dr. Lütfi Kırdar City Hospital. The study received approval from the Clinical Research Ethics Committee of Kartal Dr Lütfi Kırdar City Hospital and was conducted in compliance with the Declaration of Helsinki (Date: April 29, 2024, no: 2024/010.99/3/23). Comprehensive demographic information, complete medical and ophthalmic histories, as well as records of topical and systemic medications, were documented for all participants. All patients received a comprehensive ophthalmic evaluation, which included an examination of the ocular surface as well as the anterior and posterior segments. Written informed consent was obtained from all participants prior to inclusion in the study, covering the use of their clinical data, examination findings, and participation in required diagnostic tests in line with ethical standards. Additionally, specific written consent for the publication of anterior segment photographs was obtained from patients who underwent imaging.

Punctal evaluation and grading were performed using slit-lamp biomicroscopy, following the grading criteria established by Kashkouli et al.[1,11] Only patients with fibrotic or membranous grade 1 punctal stenosis were included in this study. The severity of epiphora was assessed objectively using the Fluorescein Dye Disappearance Test (FDDT). A fluorescein strip was moistened with a single drop of an ophthalmic antibiotic and placed into the inferior fornix. After 5 minutes, the remaining dye was evaluated under cobalt blue light and graded on a scale from 0 (complete clearance) to 4+ (full retention). The results were compared with the opposite eye, and delayed fluorescein clearance was indicative of impaired tear drainage. FDDT scores of 0 and 1 were classified as negative, whereas scores of 2 to 4 were considered positive.[12]

Furthermore, epiphora was assessed qualitatively using the Munk scale and the Lac-Q questionnaire. The Munk scale, ranging from 0 (no epiphora) to 4 (constant tearing), was used for subjective grading of symptom severity. Scores of 0 and 1 were categorized as negative, while scores from 2 to 4 were considered positive.[13] The Lac-Q questionnaire, designed to evaluate lacrimal symptoms and the social impact of the condition, was employed in this study.

The symptom section comprised 4 categories: excessive tearing, discomfort, stickiness, and swelling. Patients rated the social impact (maximum score: 5) and lacrimal symptoms (maximum score: 14 per eye) at each visit.[14] These assessments were conducted by an independent observer (AA).

Experienced surgeons MO and TY performed the procedures, including punctal dilation, canalicular probing, and nasolacrimal duct irrigation, either in an outpatient clinic or under a surgical microscope in the operating room. Before the procedure, topical anesthesia with proparacaine hydrochloride ophthalmic solution (Alcaine®, Alcon Laboratories Inc., Fort Worth, TX, USA) was administered. Depending on the degree of punctal stenosis, the punctal orifice was primarily opened using a 27-gauge needle, while a punctum finder was used in selected cases. The punctum finder was then introduced to expand the lower punctum, followed by the application of progressively larger dilators to further widen the ampulla. Once adequate dilation was achieved, a 00 Bowman probe (diameter 0.9 mm, Altomed, Tyne and Wear, England) was inserted. If a canalicular probe encountered resistance, the obstruction was classified as canalicular stenosis. Canalicular membranous stenosis was identified when a membranous soft stop could be overcome with effort, whereas a hard stop signified a patent canalicular system. Nasolacrimal duct patency was evaluated by irrigating saline through a lacrimal cannula connected to a 5 mL syringe. Unobstructed flow of saline into the nose or nasopharynx without regurgitation confirmed the system's patency. Patients with canalicular or nasolacrimal duct pathology were excluded from the study.

Following these evaluations, patients were categorized into 2 groups.

Group A-Topical Cyclosporine A Treatment: Patients with dry eye findings (Schirmer score [with or without anesthesia] of 0-10 mm/5 min or tear film break-up time ≤10 seconds) received Restasis® (Allergan, an AbbVie company, Irvine, CA, USA) cyclosporine A 0.05% eye drops twice daily for 6 months.

Group B-Rectangular 3-Snip Punctoplasty: Patients without significant dry eye disease or ocular surface pathology underwent lower punctum rectangular 3-snip punctoplasty to surgically enlarge the punctal opening. This technique involved 3 incisions: 2 vertical incisions on either side of the vertical canaliculus and one incision at the base, effectively enlarging the punctal opening.[15] Postoperative treatment in both groups included a 2-week course of topical antibiotic-steroid combination therapy due to the shared initial intervention of punctal dilation and probing, which may cause short-term inflammation. This limited topical steroid use was not expected to interfere with the long-term immunomodulatory effects of cyclosporine A eye drops.

The FDDT, Munk scale, and Lac-Q scores were recorded prior to treatment and re-evaluated at the 6th week and 6th month after either medical or surgical intervention. Functional success was characterized by a Munk score of 0 or 1 and an FDDT grade of 0 to 2, while anatomical success was defined as achieving a grade 3 punctum by the 6-month follow-up.

STATISTICAL ANALYSIS

Statistical analyses were conducted based on data from 33 eyes. Although the study initially included 33 patients (58 eyes), only the most severely affected eye was considered in bilateral cases to avoid inter-eye dependency in statistical evaluations. Data analysis was performed using SPSS for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including mean, standard deviation, median, interquartile range (25th-75th percentiles), frequency, and percentage, were utilized for data presentation. The Kolmogorov-Smirnov test was applied to determine whether the data followed a normal distribution. The Mann-Whitney U test was used for comparisons between 2 independent groups, while the Kruskal-Wallis test was applied for comparisons involving more than 2 independent groups with non-normally distributed data. The Friedman test was employed to analyze repeated measures within the same group, and "post hoc" pairwise comparisons were performed using the Wilcoxon Signed-Rank test. Categorical variables were analyzed using either the chi-square test or Fisher's Exact test, depending on data characteristics. A p value below 0.05 was considered statistically significant in all analyses.

RESULTS

A total of 54 patients were initially diagnosed with membranous or fibrotic grade 1 punctal stenosis. After undergoing punctal dilation with a 27-gauge needle or punctum finder, followed by canalicular probing and nasolacrimal duct irrigation, 13 patients were also found to have canalicular obstruction, while an additional 8 patients were diagnosed with primary acquired nasolacrimal duct obstruction. These patients were excluded from the study, leaving 33 patients with isolated severe acquired punctal stenosis for analysis. Among them, 19 had fibrosed type grade 1 punctal stenosis (Figure 1), while 14 had membranous type grade 1 punctal stenosis (Figure 2). Of the 33 patients included, 17 (51.5%) were assigned to Group A (Medical Treatment) and received Cyclosporine A 0.05% eye drops, while 16 (48.5%) were assigned to Group B (Surgical Treatment) and underwent rectangular 3-snip punctoplasty. The mean age of the participants was 58.61±10.85 years (range: 38-78 years), with no statistically significant difference between Group A (55.76±10.29 years) and Group B (61.63±10.93 years) (p=0.130). The study population consisted of 23 females (69.7%) and 10 males (30.3%), with a comparable gender distribution between the 2 groups (p=0.909). The most frequently associated pathology was blepharitis (60.6%, 20/33). Additionally, 57.6% (19/33) of patients had a history of chronic topical anti-glaucoma medication use, including beta-blockers and/or prostaglandin analogs. No significant complications were observed in either group, except for mild eye irritation in 3 patients from Group A, which resolved spontaneously within 1 week of treatment.

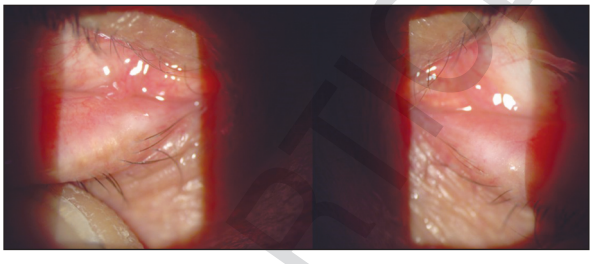

FIGURE 1: The lower external lacrimal punctum is completely covered by a fibrotic membrane.

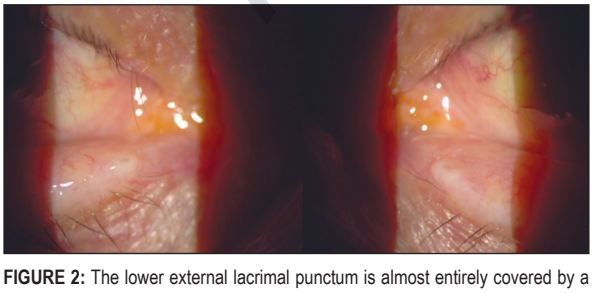

FIGURE 2: The lower external lacrimal punctum is almost entirely covered by a membranous membrane.

MUNK SCORE, LAC-Q SCORE, AND FDDT ASSESSMENTS

Munk Score, Lac-Q Score, and FDDT evaluations showed a significant reduction over time ($p<0.001$ for all). Pairwise comparisons showed a notable reduction in Munk scores from baseline to the 6th week ($p<0.001$) and from baseline to the 6th month ($p<0.001$). Furthermore, a significant decline was also observed between the 6th week and the 6th month ($p<0.001$). When comparing Group A and Group B, pre-treatment Munk scores were similar between the 2 groups ($p=0.470$). By the 6th week, Munk scores decreased in both groups, but this difference remained statistically non-significant ($p=0.249$). However, by the 6th month, Group A had significantly lower Munk scores compared to Group B ($p=0.004$). Detailed comparisons of Munk scores at baseline, the 6th week, and the 6th month between Group A and Group B are summarized in Table 1.

Pairwise comparisons indicated a notable reduction in Lac-Q scores from baseline to the 6th week ($p<0.001$), from baseline to the 6th month ($p<0.001$), and between the 6th week and the 6th month ($p<0.001$). At baseline, the mean Lac-Q scores were comparable between Group A and Group B ($p=0.507$). Although both groups demonstrated improvement by the 6th week, the difference remained statistically non-significant ($p=0.349$). A detailed comparison of Lac-Q scores at baseline, the 6th week, and the 6th month between Group A and Group B is presented in Table 2.

Pairwise comparisons demonstrated a significant reduction in FDDT scores from baseline to the 6th week ($p<0.001$), from baseline to the 6th month ($p<0.001$), and between the 6th week and the 6th month ($p<0.001$). At baseline, FDDT scores were comparable between the 2 groups ($p=0.287$). By the

TABLE 1: Munk score comparison between groups at baseline, 6th week, and 6th month

Munk score		Cyclosporine A 0.05% eye drops (n=17)	Rectangular 3-snip punctoplasty (n=16)	Z statistic	p value
Pre-treatment	$\bar{X}$±SD	3.12±0.78	2.94±0.68	-0.722	0.470
	Median [IQR]	3 (2.5-4)	3 (2.5-3)		
6th week	$\bar{X}$±SD	2.12±0.70	1.94±0.57	-0.825	0.249
	Median [IQR]	2 (2-3)	2 (2-2)		
6th month	$\bar{X}$±SD	1.00±0.50	1.63±0.62	-2.849	**0.004***
	Median [IQR]	1 (1-1)	2 (1-2)		

*Mann-Whitney U test; n: number; SD: standard deviation; IQR: Interquartile range (25th-75th percentiles)

TABLE 2: Lac-Q score comparison between groups at baseline, 6th week, and 6th month.

Lac-Q score		Cyclosporine A 0.05% eye drops (n=17)	Rectangular 3-snip punctoplasty (n=16)	Z statistic	p value*
Pre-treatment	$\bar{X}$±SD	9.00±1.54	8.63±1.41	-0.644	0.507
	Median [IQR]	9 (8-10)	8.5 (7.5-9.5)		
6th week	$\bar{X}$±SD	5.12±0.93	4.81±0.75	-0.936	0.349
	Median [IQR]	5 (4-6)	5 (4-5)		
6th month	$\bar{X}$±SD	1.88±0.86	2.00±0.82	-0.307	0.759
	Median [IQR]	2 (1-2)	2 (1-3)		

*Mann-Whitney U test; n: number; SD: standard deviation; IQR: Interquartile range (25th-75th percentiles)

6th week, Group A exhibited a significantly lower FDDT score compared to Group B (p=0.002). However, at the 6th month, the difference between the groups was no longer statistically significant (p=0.200). Table 3 provides a detailed comparison of FDDT scores between Group A and Group B at baseline, the 6th week, and the 6th month.

EVALUATION OF FUNCTIONAL AND ANATOMICAL SUCCESS

The functional success rate was higher in Group A (76.5%, 13/17) compared to Group B (43.8%, 7/16), with the difference being borderline significant (p=0.052, χ^2 test). Patients in Group A had 4.18 times higher odds of achieving functional success than those in Group B, but this association did not reach statistical significance (OR=4.18, 95% CI: 0.94-18.61). Anatomical success was achieved in 7 of 17 patients (41.2%) in Group A and 7 of 16 patients (43.8%) in Group B (Figure 3). The difference between the 2 groups was not statistically significant (p=0.881). 7 out of 33 eyes (21.2%) exhibited punctal restenosis, with 4 cases in Group A and 3 cases in Group B. Notably, all cases of restenosis had previously been classified as fibrosed type grade 1 punctal stenosis. However, there was no statistically significant difference in restenosis rates between the 2 groups (p=1.000).

TABLE 3: Comparison of FDDT scores between groups at baseline, 6th week, and 6th month

FDDT		Cyclosporine A 0.05% eye drops (n=17)	Rectangular 3-snip punctoplasty (n=16)	Z statistic	p value
Pre-treatment	$\bar{X}$±SD	3.35±0.49	3.13±0.62	-1.065	0.287
	Median [IQR]	3 (3-4)	3 (3-3.5)		
6th weeks	$\bar{X}$±SD	1.53±0.62	2.13±0.34	-3.052	**0.002***
	Median [IQR]	1 (1-2)	2 (2-2)		
6th months	$\bar{X}$±SD	1.18±0.73	1.50±0.52	-1.281	0.200
	Median [IQR]	1 (1-2)	1.5 (1-2)		

*Mann-Whitney U test; FDDT: Fluorescein Dye Disappearance Test; n: number; SD: standard deviation; IQR: Interquartile range (25th-75th percentiles)

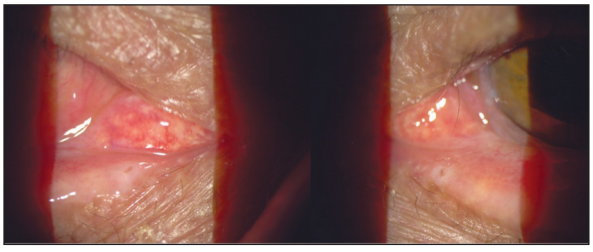

FIGURE 3: The punctal orifice was initially opened using a 27-gauge needle to expand the lower punctum. A fully patent grade 3 punctum is observed after 6 months of topical cyclosporine A 0.05% treatment.

DISCUSSION

To the best of our knowledge, this is the 2nd study investigating the efficacy of topical cyclosporine A 0.05% ophthalmic solution in acquired punctal stenosis. Nassief et al. previously reported a functional success rate of 95.2% and an anatomical success rate of 57.1% at 6 months, with functional outcomes surpassing those of the mini-Monoka stent group.[10] Although our overall success rates were lower, we similarly found higher functional success in the cyclosporine drop group (76.5%) compared to punctoplasty (43.8%). Although this difference was borderline significant, larger patient cohorts and longer follow-up studies may further establish the statistical significance of these findings. These results suggest that functional improvement in punctal stenosis treatment may not solely depend on anatomical correction but also on addressing underlying inflammatory mechanisms, where cyclosporine A plays a key role. Acquired punctal stenosis has been reported to show a female predominance in several studies, ranging from 65% to 71%.[16-18] In our study, female patients accounted for 69.7% of cases, aligning with previous reports. This gender disparity has been attributed to hormonal influences in earlier studies.[16,17] Interestingly, all cases of restenosis (21.2%) were observed in patients with fibrosed-type punctal stenosis, suggesting that fibrosis severity may influence restenosis risk. Fibrotic changes in the punctal tissue could lead to persistent inflammation, delayed wound healing, and an increased likelihood of recurrent obstruction. Further studies with larger cohorts are needed to establish a definitive association between fibrotic severity and restenosis.

Snip punctoplasty, one of the oldest and most commonly performed procedures (1- to 4-Snip), is often associated with scarring and re-adhesion, potentially leading to anatomical distortion and lower success rates.[19] Among its variations, rectangular 3-snip punctoplasty has shown the highest success rates, better preserving anatomical integrity and lacrimal pump function. Chak and Irvine reported an 89.8% success rate, comparable to triangular 3-snip punctoplasty.[15] Ali et al. found that after 6 months, 74.7% had complete symptom resolution, while 10.3% had persistent epiphora, and 5.7% had recurrent stenosis.[6] Taskiran Comez et al. introduced the Punctoplasty With Canalicular Triangular Flap, achieving over 90% success with no restenosis.[18] In our study, however, the anatomical and functional success rate of punctoplasty was relatively lower, around 40%. This could be attributed to the higher severity of punctal stenosis in our patient group, the presence of fibrotic-type grade 1 punctal stenosis in nearly 2/3's of the patients, and chronic blepharitis findings in more than half of the cases. Additionally, long-term use of anti-glaucoma eye drops may have played a role in these outcomes.

Topical cyclosporine A 0.05% eye drops were introduced to the market in 2003 and have since been approved by the FDA for the treatment of dry eye disease.[20] Numerous studies have demonstrated their efficacy and safety in managing various ocular surface diseases. Given that chronic inflammation plays a key role in the pathogenesis of these conditions, the therapeutic mechanism of cyclosporine A is well supported.[21] As a potent immunomodulatory agent, cyclosporine A suppresses ocular surface inflammation, enhances tear film stability, and may improve functional tear drainage by maintaining ocular surface integrity and modulating tear production.[10] Anatomical success is typically defined as the restoration of lacrimal system patency. However, functional success, measured by symptom relief and improved tear drainage, depends on multiple factors beyond structural patency. Although punctoplasty creates an anatomically open punctum, it does not guarantee effective tear drainage due to potential disruptions in lacrimal pump function. This highlights the complexity of the lacrimal drainage system,

where anatomical patency alone may not always result in symptom relief. Our findings further support this distinction, as cyclosporine A 0.05% eye drops and rectangular 3-snip punctoplasty demonstrated similar anatomical success rates, yet functional success was significantly higher in the cyclosporine A group, likely due to its anti-inflammatory effects.

The significantly lower FDDT score in Group A at 6 weeks compared to Group B may be due to cyclosporine A's early anti-inflammatory effect. While cyclosporine A suppresses T-cell-mediated inflammation and reaches peak efficacy within 3 months, mild peripunctal inflammation in the early postoperative period may temporarily affect tear outflow. In contrast, punctoplasty patients may have experienced persistent edema and surgery-induced inflammation, further impairing lacrimal drainage. These factors likely contributed to the observed differences in FDDT scores.

The study has some limitations, including a small sample size and lack of randomization. Additionally, the inclusion of grade 1 punctal stenosis limited the ability to measure punctal size either manually or using optical coherence tomography. Future long-term, randomized, and comparative studies are needed to better evaluate the benefits of adding cyclosporine A to punctoplasty, particularly regarding its impact on surgical outcomes and functional success.

CONCLUSION

Topical cyclosporine A 0.05% eye drops demonstrated greater functional success than punctoplasty, despite similar anatomical outcomes, highlighting the role of inflammatory modulation in managing grade 1 acquired punctal stenosis. Given the persistence of functional epiphora and the risk of restenosis following punctoplasty, minimally invasive alternatives such as cyclosporine A may serve as a promising treatment option. Further extensive studies with prolonged follow-up are required to assess its long-term effectiveness and potential integration into clinical practice.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Murat Oklar, Anıl Ağaçkesen;* ***Design:*** *Murat Oklar, Anıl Ağaçkesen, Gizem Kardaş;* ***Control/Supervision:*** *Murat Oklar, Titap Yazıcıoğlu;* ***Data Collection and/or Processing:*** *Murat Oklar, Anıl Ağaçkesen;* ***Analysis and/or Interpretation:*** *Murat Oklar, Anıl Ağaçkesen, Gizem Kardaş;* ***Literature Review:*** *Murat Oklar, Anıl Ağaçkesen, Raziye Dönmez Gün;* ***Writing the Article:*** *Murat Oklar, Titap Yazıcıoğlu;* ***Critical Review:*** *Murat Oklar, Titap Yazıcıoğlu;* ***References and Fundings:*** *Murat Oklar, Gizem Kardaş, Raziye Dönmez Gün;* ***Materials:*** *Murat Oklar, Gizem Kardaş, Raziye Dönmez Gün.*

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