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# Topical Cyclosporine-A for Management of Epiphora in Eyes with Acquired Punctal Stenosis

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## Abstract

**Background:** Cyclosporine A (CsA) is an inhibitor of calcineurin that prevents T-cell production of inflammatory cytokines and disrupts the immune-mediated inflammatory response that plays a crucial mechanism in punctal stenosis. **Purpose:** To evaluate the clinical outcomes and tolerances of CsA in treating epiphora in eyes with punctal stenosis. **Study Design**: Prospective study. **Methods:** The study included patients who presented with symptomatic epiphora associated with lower punctal stenosis during the period between July 2019 and December 2020. Patients were treated with topical 0.05% CsA on twice daily dose with topical preservative-free artificial tears Q.I. D. Patients were followed up monthly for at least 3 months by Munk epiphora grading, Fluorescein dye disappearance test (FDT) and evaluation of the patient satisfaction. **Results:** A total of 26 patients with 47 eyes were included in the study with a mean age of 55.1 ± 10.24 years. All the eyes had grade 0 lower punctal stenosis with grade 4 on Munk grading and grade 3 in FDT. There was a statistically significant difference in the Munk grading and FDT along the follow-up period compared to the baseline values ($p < 0.001$). Patient's satisfaction was complete in 7 (26.9%) patients in the first month and 19 (73%) by the 3rd month. None of the patients encountered any complications during treatment. **Conclusion:** CsA can control the inflammation of the conjunctival sac and restore the integrity of the ocular surface with subsequent symptomatic relief of the epiphora in eyes with punctal stenosis.

## Keywords

Cyclosporine A, Epiphora, Munk Grading, Ocular Surface, Punctal Stenosis

## 1. Introduction

Epiphora related to lacrimal outflow obstruction affects a wide range of patients. It adversely affects their quality of life by causing blurred vision, ocular and peri-ocular tissue irritation beside likely social embarrassment [1].

Punctal stenosis prompts epiphora in nearly 94% of the patients [2]. Acquired punctal stenosis is a condition in which the external opening of the lacrimal canaliculus is narrowed or occluded which may be also associated with ductal stenosis. In most cases, the early response to different noxious stimuli is usually punctal occlusion due to edema followed by conjunctival overgrowth and later keratinization and cicatricial punctal stenosis. Punctum stenosis may result from inflammatory or infectious eye disease, systemic or topical drug toxicity, lid malposition, different forms of trauma, tumors or ageing changes [3] [4].

In eyes with partial punctal stenosis, Mini-monoka puncto-canaliculo-plasty is an effective, safe, simple and relatively non-invasive treatment strategy for the management of epiphora secondary to punctal and/or canalicular stenosis [5]. However, clinical studies have not demonstrated their long-term success. Considerable experience with surgical snip procedures had proposed the preference for their utilization in the treatment of such cases [6] [7] [8]. All these procedures hang on the presence of a landmark for the stenosed punctum. In cases of complete obstruction, it could be challenging to identify the exact site of the punctum with an additional burden during management. Moreover; surgery might not be a suitable choice for some patients, particularly in the elderly population.

Although there are many suggested etiologies for punctal stenosis, some patients encounter this disorder even without any relevant history. Whatever the possible trigger etiology, inflammation plays a crucial mechanism in punctal stenosis [9].

Cyclosporine A (CsA) is an inhibitor of calcineurin—an activator of T-cells—and it prevents T-cell production of inflammatory cytokines and disrupts the immune-mediated inflammatory response [9] [10]. The immunomodulatory activity of CsA reduces the inflammation associated with the corneal and conjunctival epithelium, accessory lacrimal glands, and subconjunctival tissues and increases conjunctival goblet cell density [11] [12].

The current study aimed to evaluate the clinical outcomes and tolerances of Cyclosporine A (CsA) in treating epiphora in eyes with complete punctal stenosis.

## 2. Methods

A prospective study included patients who were referred to our outpatient clinics in the Farwanyia hospital in Kuwait during the period between July 2019 and December 2020, having symptomatic epiphora associated with severe acquired lower punctal stenosis.

The study was approved by the Institutional Review Board Regulations (IRB) of the Kuwait Ministry of Health, and followed the Declaration of Helsinki. The study was registered in clinical trial, Gov (code NCT04637633). Eligible patients

signed an informed consent form prior to enrollment. Adult patients were eligible for participation if they had a diagnosis of grade 0 punctal stenosis with epiphora that persisted for more than three months both indoors and outdoors, and who refuse surgical interference or injection of Botulinum toxin (Botox) in the lacrimal gland.

Exclusion criteria included congenital punctal obstruction, acute edematous puncti, history of dacryocystitis, and inflammatory systemic diseases. Patients with other causes of epiphora, lid laxity, entropion, and ectropion were excluded. Patients with previous eyelid or lacrimal drainage surgery, untreated conjunctivitis or blepharitis were also excluded.

Demographic data including age, gender, laterality, medical history, topical and systemic treatments, and symptoms were obtained and recorded. Munk scale for epiphora grading was used (**Table 1**) [13]. Routine slit lamp examination was carried on with special focus on the height of the tear meniscus, position of the lid margin, meibomian glands (MG), tear break up time (TBUT) in minutes and state of the conjunctiva. The level of punctal stenosis was evaluated clinically by a visual grading system for the assessment of external lacrimal punctum, as described by Kashkouli *et al.* [14], Fluorescein dye disappearance test (FDT) was performed via installing a drop of 2% fluorescein and asses after 3 and 5 min of the remaining dye in the tear meniscus.

All patients were treated with topical 0.05% CsA (Restasis®, Allergan Inc, Irvine, California) on twice daily dose, in addition to the topical preservative free artificial tears Q.I. D. Patients were followed up monthly for at least 3 months by epiphora grading, FDT (as follows: grade 1 = 3 min, grade 2 = 3 - 5 min and grade 3 ≥ 5 min) and measuring the patient satisfaction (categorized as not satisfied = 0, partial satisfaction = 1 and complete satisfaction = 2). Syringing was not done in any of the patients included in the study due to complete stenosis of the puncti.

## 3. Statistical Analysis

Data was analyzed using SPSS version 16 (Chicago, USA) software. Wilcoxon Rank test was used to detect the difference between pre- and postoperative ordinal data in the study group. Mc Nemar's test was used to compare categorical data. Significance was considered at $p < 0.05$.

**Table 1.** Munk score [13].

| Grade | Clinical finding |
|---|---|
| 0 = No epiphora | |
| 1 = Occasional epiphora requiring drying or dabbing less than twice a day | |
| 2 = Epiphora requiring dabbing two to four times per day | |
| 3 = Epiphora requiring dabbing five to ten times per day | |
| 4 = Epiphora requiring dabbing more than ten times daily or constant tearing | |

## 4. Results

A total of 26 patients with 47 eyes were included in the study. Eleven females and 15 males with mean ± SD age of 55.1 ± 10.24 years (29 - 68 years). Mean follow-up time was 5.3 ± 1.5 months (3 - 8 months). Smoking was reported by 11 (42%) patients and history of non-specific allergy in 7 (34.6%) patients.

Conjunctival hyperemia was present in almost half of eyes (23/47). Bilateral involvement was recorded in 21 patients (81%). Five patients had only unilateral punctal stenosis: 4 in the right eye and one in the left eye. Based on the punctal grading system; all the included eyes had severe lower punctal stenosis (grade 0) with grade 4 on Munk grading and grade 3 in FDT. Under slit-lamp examination, all patients exhibited normal TBUT with clear cornea. Conjunctival papillae were found in 15 eyes (32%), conjunctival hyperemia in 23 (47%), MG obstruction in14 (30%) and Peri-ocular dermatitis in 38 (81%). The baseline mean ± SD of Tear break up time (TBUT) was 13.8 ± 1.36 sec (**Table 2**).

**Table 3** illustrates the distribution of patients according to their Munk grading for epiphora and FDT along the follow-up period. At baseline; 100% of the patients had grade 4 Munk grading. In the 3rd month, 35 (74%) had grade 1and 12 (26%) had grade 0. There was a statistically significant difference in the Munk grading and FDT along the follow-up period compared to the baseline values ($p < 0.001$). Patients' satisfaction was complete in 7 (26.9%) patients in the first month raised to 19 (73%) by the 3rd month.

In 3rd month, the number of eyes with hyperemia statistically decreased to 16 (34%) and the number of eyes with periocular dermatitis decreased from 38 (81%) to 20 (42.5%) ($p = 0.031$ & $p < 0.001$ respectively, Mc-Nemar's test). None of the eyes retained manifestations of MGD by the end of the follow up. None of the patients encountered any serious complications during treatment except for the foreign body sensation during the first 15 day in 6 patients (23%) that improved later during the follow-up period.

## 4. Discussion

Epiphora in adults is commonly a combination of the eyelid, ocular surface and lacrimal factors. Almost all the patients encounter a mix of underlying causes including dry eye, meibomian gland dysfunction, and allergy combined with variable grades of lacrimal drainage pathway obstruction. Basically, a healthy ocular surface is the cornerstone in reducing symptomatic epiphora [15].

Topical Cyclosporine-A (CsA) was initially proposed to improve the subjective symptoms as well as the objective signs in patients with keratoconjunctivitis sicca. Improved tear break-up time, and both corneal and conjunctival staining scores were reported following its application [16]. CsA has also been proposed in the treatment of meibomian gland dysfunction, dry eye disease, rosacea and allergy since all these conditions are believed to have inflammation as an underlying component of reflex tearing [17].

Based on this knowledge we conducted a prospective study to assess the possibility

**Table 2.** Demographic and baseline clinical data of the studied patients.

| Characteristics | n (%) |
|---|---|
| **Total number (patients/eyes)** | 26/47 |
| **Gender (n of patients)** | |
| Male | 15 (57.7%) |
| Female | 11 (42.3%) |
| **Age (years)** | |
| Mean ± SD | 55.1 ± 10.24 |
| (min-max) | (29 - 68) |
| **Follow up period** (months) | |
| Mean ± SD | 5.3 ± 1.5 |
| (min-max) | (3 - 8) |
| **Associated Symptoms** | |
| Itching | 15 (32%) |
| Burning sensation | 22 (47%) |
| Blurring of vision | 38 (81%) |
| Redness | 23 (47%) |
| **Baseline Examination** | |
| Number of Lower punctal involvement | 47 (100%) |
| Number of upper punctal involvement | 42 (89%) |
| Conjunctival papillae | 15 (32%) |
| Conjunctival hyperemia | 23 (47%) |
| MG obstruction | 14 (30%) |
| Peri-ocular dermatitis | 38 (81%) |
| TBUT (mean ± SD, sec) | 13.8 ± 1.36 |

n = number; SD = standard deviation; min-max = minimum-maximum; MG = meibomian gland; TBUT = tear break up time; sec = seconds.

**Table 3.** Pre- and post-treatment Munk grading of epiphora and Fluorescein disappearance test among the studied group.

| Timing | Munk grading for epiphora | | | | | Fluorescein disappearance test | | |
|---|---|---|---|---|---|---|---|---|
| | Gr 4 N (%) | Gr3 N (%) | Gr2 N (%) | Gr1 N (%) | Gr0 N (%) | Gr1 N (%) | Gr2 N (%) | Gr3 N (%) |
| Pre | 47 (100) | -- | -- | -- | -- | -- | -- | 47 (100) |
| 1 m | 6 (13) | 32 (68) | 9 (19) | -- | -- | -- | 36 (77) | 11 (23) |
| 2 m | -- | 6 (13) | 8 (17) | 22 (47) | 11 (23) | 32 (68) | 8 (17) | 7 (15) |
| 3 m | -- | -- | -- | 35 (74) | 12 (26) | 33 (70) | 14 (30) | -- |

Pre = pretreatment; N = number of eyes; gr = grade; m = month.

of the use of topical CsA in treating epiphora in eyes with acquired severe punctal stenosis. The study included 47 eyes of 26 patients with grade 0 punctal stenosis who were treated by daily twice application of CsA and lubricants for 3 months. The main outcome was the change in the Munk grading of epiphora and the fluorescein disappearance test at the end of the follow-up period.

There was a statistically improvement regarding both the subjective and the objective grading of the epiphora after 3 months as well as improvement of the conjunctival hyperemia, periocular dermatitis and MGD. There was an increase in the patients' satisfaction during the follow-up period through the punctal stenosis remained unchanged.

One possible mechanism is that the punctal stenosis might be a result of a generalized inflammatory condition affecting the conjunctiva, punctum and the canaliculi with punctal stenosis developing as a late consequence. The resultant delayed tear clearance might in turn set a vicious circle exacerbating the pre-existing ocular surface inflammation with more irritation, T-cell activation and cytokines release which induction of more inflammation and so on. CsA prevents the T-cells from entering this battle thus terminating this cycle at this level [17].

Yet, until the results of two histopathological studies; few data were documented about the underlying pathophysiologic processes of acquired punctal stenosis [18] [19]. In those studies; specimens from the puncti were examined showing evidence of chronic inflammation in the majority of specimens (83 and 100 % of the cases). In a later published study, 97.2% of the conjunctival specimens displayed inflammatory infiltrates, which further validates the prior results regarding the proposed inflammatory mechanism of acquired punctal stenosis [20]. Outstandingly, all patients in their study were diagnosed with presumed idiopathic punctal stenosis.

Old age per se is considered a risk factor for punctal stenosis, with increased prevalence reported in patients between 40 and 70 years of age. The mean age of our cohort was 53.8 ± 11.8 years, which coincides with previously reported cases [21]. This association is possibly due to aging changes which render the punctum a less resilient dense fibrous structure. It may also affect the orbicularis fibers driving it more atonic with ensuing punctal stenosis [22]. Pharmacologic treatment for this age group is a reasonable adjuvant in the developing armamentarium for symptomatic treatment.

The literature mostly described female predominance in punctal stenosis which may be related to the postmenopausal hormonal changes [23] [24], though Bukhari found no gender predilection [25]. The astonishingly male preponderance in our study (83.3%) has not been reported in previous studies, perhaps because they included other etiologies of punctal stenosis.

The anti-inflammatory role of CsA may acts hand in hand with the normal autoregulatory mechanism that controls the tear production from the lacrimal glands. It is postulated that, as long as the tears are not cleared, the feedback signal is truncated, thereby the secretion of tears will stop, and eventually no overflow of

tears will be encountered [26]. However, this autoregulatory mechanism may be defective in patients with ocular irritation, because they have been noted to have decreased corneal sensitivity scores [27]. Thus, re-establishing the normal ocular surface integrity using CsA might aid in restoring this downregulatory pathway hence diminishing the epiphora.

Another implicated factor was the associated allergic conditions. This is often seen in eyes with allergic dermato-conjunctivitis in which there was keratinization of the eyelid where punctal stenosis and edema are often noticed. Although more than half of our patients gave a history of non-specific allergy, a diagnosis of allergic conjunctivitis in our patients was dubious since only conjunctival papillae were present in 4 eyes of 2 patients. Yet, CsA may have also played a role in such cases owing to its reported promising results in allergic conjunctivitis [28].

To our knowledge, this is the first clinical trial for the use of topical CsA in treating epiphora in eyes with complete punctal stenosis. There are some shortcomings in the current study including the small number of cases with the short follow-up period, which could not reflect the long-term effect of CSA on the lacrimal system.

Cyclosporine A may exert a short-term impact on the lacrimal system. CsA can treat the inflammation of the conjunctival sac and restore the integrity of the ocular surface with subsequent symptomatic relief of the epiphora in the eyes with punctal stenosis. Moreover, the effect of CSA is not reflected only in symptomatic relief of lacrimal drainage system obstruction, but also in the interaction between the secretory and the drainage systems. However, the exact mechanism of action and possible longer-term effects need to be proven.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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