Original Article

Topical Cyclosporine A for Treatment of Dry Eye Due to Chronic Mustard Gas Injury

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Abstract

Purpose: To evaluate the efficacy of topical cyclosporine A (tCsA) for treatment of dry eye disease in patients suffering from chronic ocular complications of mustard gas (MG) injury.
Methods: This interventional case series included patients with MG injury suffering from severe dry eye despite receiving artificial tears and punctal plugs. Patients were administered tCsA 0.05% twice daily for 3 months. Severity of the condition was evaluated by measuring tear osmolarity, ocular surface disease index (OSDI), tear break-up time (TBUT), and Schirmer's test at baseline and at the end of study.
Results: A total of 34 patients with chronic MG injury and mean age of 47.1 ± 6.5 years were studied. Compared to baseline values, tear osmolarity (301.7 ± 11.5 vs. 286.3 ± 7.9 mOsmol/L, $P < 0.001$) and OSDI (47.5 ± 7.2 vs. 42.7 ± 7.1, $P < 0.001$) were significantly improved. Likewise, Schirmer's test (4.6 ± 1.3 vs. 5 ± 1.3 mm, $P < 0.001$) and TBUT (1.9 ± 1.4 vs. 2.7 ± 1.5 s, $P < 0.001$) also significantly recovered at the end of the study.
Conclusion: TCsA 0.05% reduces tear osmolarity and improves dry eye symptoms and can serve as an efficacious treatment for ocular complications in patients with chronic MG injury.

Keywords: Cyclosporine A; Dry Eye Syndrome; Mustard Gas; Tear Osmolarity

J Ophthalmic Vis Res 2014; 9 (4): 417-422.

INTRODUCTION

Late ocular complications of sulfur mustard gas (MG) are very common among intoxicated individuals. Ocular toxicity of MG often manifests as dry eye and decreased tear meniscus.[1-4] Victims of MG exposure experience symptoms of dry eye disease such as burning, itching, foreign body sensation, photophobia, red eye, and reduced visual acuity.[1,5] These symptoms have a negative impact on patients' daily activities and quality of life, and thus require effective management.[6,7]

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Received: 15-07-2013 Accepted: 18-01-2014

Susceptibility of the eyes to the toxic effects of MG is due to moistness of the ocular surface that allows rapid cyclization and activation of the agent, in addition to the high turnover and metabolic rate of corneal epithelial cells that increase their sensitivity to the lipophilic sulfur mustard trapped into the oily tear layer. The most frequent destructive ocular complications of MG injury include chronic blepharitis, decreased tear meniscus, limbal ischemia and conjunctival vascular abnormalities.[5] MG-induced keratitis may be

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DOI: 10.4103/2008-322X.150803

persistent leading to corneal degeneration, or progress in a silent manner to severe ocular lesions.[5] While the pathophysiology of MG-induced keratitis remains obscure, an autoimmune reaction to corneal antigens has been suggested to play a central role in the development of this disease and causes severe limbal and corneal damage.[7-9]

Although various strategies are employed in the treatment and management of dry eye disease, currently available medications have limited efficacy in controlling the symptoms, especially in cases secondary to sulfur mustard (SM) exposure.[10] Hence, there is an urgent demand for novel therapeutic approaches in patients suffering from late ocular complications of SM. Recent studies have suggested a key role for an underlying inflammatory component in the pathogenesis of dry eye disease. This has led to the use of many anti-inflammatory-based therapies, such as short-term corticosteroids and long-term cyclosporine, to improve the efficacy of treatment in these patients.[11,12] Thus far, several lines of evidence have favored the effectiveness of topical cyclosporine A (tCsA) in the treatment of dry eye disease due to varying etiologies.[13-17] However, tCsA has not yet been tested in patients with late ocular complications of MG. The present study was undertaken to investigate the effects of tCsA in a group of MG-exposed patients suffering from severe dry eye disease.

METHODS

This prospective interventional case series included 36 MG-exposed male veterans suffering from symptoms of dry eye disease despite receiving artificial tear and punctal plugs. Inclusion criteria were ocular surface disease index (OSDI) score of ≥ 0.25 and Schirmer's test (with anesthesia) <10 mm. All subjects underwent a thorough ocular examination including slit lamp biomicroscopy and visual acuity measurement using a logMAR chart (at 3 m testing distance). For each patient, only the more severely affected eye was included in the study. Exclusion criteria were the presence of active ocular infection, history of ocular surgery within the past 3 months, and a history of hypersensitivity to cyclosporine A. Individuals with any systemic diseases that may cause dry eye, such as diabetes mellitus, rheumatologic disorders and Sjögren's syndrome were also excluded. The Ethics Committee at Baqiyatallah University of Medical Sciences approved the study protocol and written informed consent was obtained from all participants.

All participants were asked to stop using any previous topical medication. One drop of tCsA 0.05% (Restasis, Allergan Inc, Irvine, CA, USA) twice daily and one drop of preservative-free artificial tear (Artelac Advanced, Bausch and Lomb GmbH, Germany) every 6 hours were prescribed for each eye for a period of 3 months. Patients were encouraged to continue their medication and were advised to report any adverse effect during the follow-up period. Participants were informed that they might experience a burning sensation during the initial weeks of therapy. During the study period, patients were contacted every 3 weeks to assure their compliance with the medication and lack of adverse effects. After 3 months, all patients were re-examined using the same tests as the first visit.

Assessment of dry eye severity was performed at baseline and at the end of the study using tear osmolarity assay, OSDI, Schirmer's test and tear break-up time (TBUT). Ocular surface staining with rose bengal or fluorescein was not performed in this study. The reason is that apart from the subjective nature of staining results, many patients with MG-induced keratitis have varying degrees of limbal stem cell deficiency which can affect the staining result independent of dry eye disease. Therefore, staining results may not be reliable in patients with MG-induced dry eye.

Tear Osmolarity Measurement

Patients were asked not to instill any drop in their eyes at least 1 hour prior to the test. Measurement of tear osmolarity was performed using an automated device (TearLab Osmolarity System, TearLab Corp., San Diego, CA, USA). This device can determine tear osmolarity with sample volumes as low as 50 nL with no need for additional calibration of the instrument as a coefficient of variation of 1.5% and analytical standard variation of ± 5.0 mOsmol/L allows performing the test just once with a high level of validity.

Ocular Surface Disease Index

A Persian translation of OSDI was applied which consists of 12 questions measuring the severity of dry eye symptoms. The OSDI score was calculated using methods described previously.[18]

Schirmer's Test

To determine the Schirmer's score, a standard Schirmer's test strip was placed in the temporal third of the lower eyelid for 5 minutes and the length of the wet part was measured in millimeters. Prior to the test, one drop of proparacaine (Alcaine, Alcon Laboratories, TX, USA) was instilled in the eyes to measure basic tear secretion.

Tear Break-Up Time Test

To conduct the TBUT test, a fluorescein strip moistened with a drop of saline solution was placed on the inferior palpebral conjunctiva. The elapsed time before the initial break-up of tear film was counted in seconds. The test was repeated three times and the mean was reported as TBUT.

Statistical Analysis

Statistical analysis was performed using SPSS software version 18 (SPSS, Inc., Chicago, IL, USA). Given the normal distribution of data, paired-samples *t*-test was used for pre-and post-treatment comparisons. Bivariate associations between baseline and post-treatment values of the evaluated parameters as well as their changes during the course of the study were assessed using Pearson's (in case of normally distributed data) or Spearman's (in case of non-normally distributed data) correlation coefficients. $P < 0.05$ were considered as statistically significant.

RESULTS

A total of 36 eyes from 36 patients with mean age of 47.1 ± 6.5 years were included in this study. Two patients (5.6%) failed to complete the treatment period with tCsA. Reasons for drop-out were respiratory complications due to MG exposure which made it impossible to continue the study in one case and severe burning sensation and blurred vision after instillation of tCsA in another patient. These two cases were excluded from statistical analysis. Mean time from exposure to MG was 26.5 ± 0.7 years. All subjects were previously using preservative-free artificial tears for treatment of dry eye and 23 (63.9%) of them had undergone punctal plugging. The most common symptom was blurred vision (83.3%) followed by ocular itching (72.2%). Slit lamp examination of the conjunctiva and cornea revealed abnormal findings such as corneal opacity in 13 (36.1%) cases, limbal ischemia affecting at least one-third of the limbus in 11 (30.1%) cases, and corneal vascularization in 10 (27.7%) cases.

Figure 1 shows the outcome measures before and after treatment. Best corrected visual acuity improved from 0.5 ± 0.2 LogMAR at baseline to 0.4 ± 0.2 LogMAR at the end of the study ($P = 0.001$). Mean OSDI score was 47.5 ± 7.2 at baseline and 42.7 ± 7.1 at the end of study ($P < 0.001$). There was a significant increase in Schirmer test scores from baseline (4.6 ± 1.3 mm) to the end of the study (5.0 ± 1.3 mm) ($P < 0.001$). tCsA therapy was associated with a significant decrease in tear osmolarity (from 301.7 ± 11.5–286.3 ± 7.9 mOsmol/L, $P < 0.001$), and a significant increase in TBUT (from 1.9 ± 1.4–2.7 ± 1.5 s, $P < 0.001$).

Overall, the majority of patients experienced improved symptoms associated with each evaluated efficacy measure. The proportion of patients with an improved score in Schirmer's test, visual acuity and TBUT at the end of the study were 61.8%, 35.3% and 50%, respectively. The proportion of patients with an increased score in Schirmer's test, visual acuity and TBUT at the end of the study were 61.8%, 35.3% and 50%, respectively. Also, the majority of patients (85.3%) had

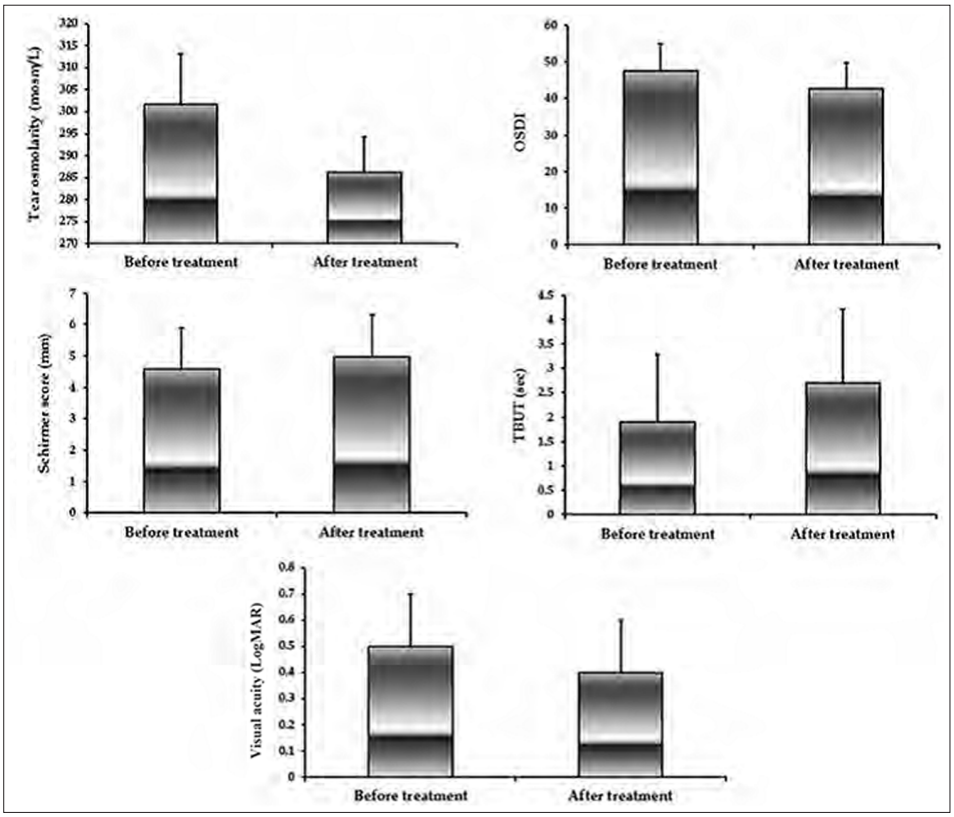

Figure 1. Dry eye parameters before and after treatment with topical cyclosporine A. Values are mean±standard deviation. OSDI, ocular surface disease index; TBUT, tear break-up time; LogMAR, logarithm of the minimum angle of resolution.

decreased tear osmolarity and OSDI score at the end of study as compared to baseline [Figure 2].

DISCUSSION

The morbidity associated with chronic complications of MG injury in different organs of the body necessitates attempts to find effective therapies to control the symptoms and correct the underlying biochemical imbalances following intoxication.[19-29] The present study aimed to investigate the efficacy of tCsA 0.05% for treatment of severe dry eye in a group of veterans suffering from late ocular complications due to MG exposure. Our primary efficacy measure was the change in tear osmolarity as the most specific and accurate test for monitoring treatment efficacy. There is compelling evidence supporting that tear osmolarity has the highest correlation with the severity of dry eye disease.[30-33] Tear film hyperosmolarity has been shown to play a critical role in the pathophysiology of aqueous tear deficiency and evaporative dry eye, and is directly connected to the etiology of disease manifestations.[34]

In this study, all patients had previous history of treatment with preservative-free artificial tears. After 3 months of tCsA 0.05% (twice daily) treatment plus preservative-free artificial tears (four times daily), all subjective (OSDI score) and objective (Schirmer score, TBUT, tear osmolarity) parameters used for assessing dry eye improved significantly. As a late complication of exposure to MG, severe dry eye is common among exposed individuals and affects their quality of life.[1,4] Two important elements in the pathogenesis of dry eye disease are eyelid inflammation and loss of conjunctival goblet cells, both leading to tear film instability and decreased tear meniscus.

Several studies have supported the efficacy of tCsA in improving signs and symptoms in different stages of dry eye disease.[13,16,17] Nevertheless, to the best of our knowledge, no study has yet been conducted on patients with MG-induced disease. Stevenson et al[13] showed the efficacy of tCsA at different concentrations in decreasing rose bengal staining, superficial punctuate keratitis, and symptoms of ocular discomfort in patients with moderate to severe keratoconjunctivitis sicca. They reported that the 0.05% concentration is associated with the highest rate of improvement. Sall et al[14] compared treatment with tCsA 0.05%, 0.1%, or vehicle twice daily in 877 patients with moderate to severe dry eye. They found that both objective (corneal fluorescein staining and Schirmer's values) and subjective measures of dry eye significantly improved in patients treated with tCsA (0.05 or 0.1%) as compared to those treated with vehicle. Perry et al[16] also reported that tCsA is effective in all stages of dry eye disease, with most improvement of symptoms in mild stages and greatest alleviation of signs in severe stages. There is also evidence indicating that tCsA is effective in increasing goblet cell density in patients with dry eye disease.[35] In a study by Moon et al[36] cyclosporine was found to be more effective in improving objective parameters of dry eye such as TBUT and goblet cell density than artificial tears. Also, the results of a trial by Pflugfelder et al[37] revealed that cyclosporine emulsion, but not artificial tears, was effective in increasing goblet cell density in patients with dry eye. The use of tCsA for the treatment of dry eye has also been evaluated in different situations associated with this syndrome i.e., in patients undergoing LASIK or in patients with dry eye associated with graft versus host disease after stem cell transplantation.[14,15]

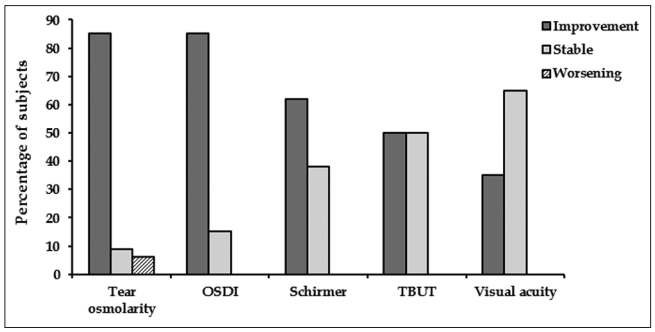

Figure 2. Proportion of subjects with improved stable or worsened score for each efficacy measure. OSDI, ocular surface disease index; TBUT, tear break-up time.

Objective measurement of the effectiveness of an applied medication on dry eye has always been a great challenge, as many of the tests do not reflect the patients' symptoms.[38,39] In many of these methods such as Schirmer's test or rose bengal staining, physical endpoints are used which reflect end-stage disease and have low positive predictive values (PPV). Researchers have shown that tear osmolarity is a test with the highest PPV and the most accurate one for diagnosis as well as follow-up of dry eye disease.[30,31,40] The automated TearLab osmolarity system that was employed in the current study is an easy-to-use system which requires a very small amount (about 50 nL) of tear and can appropriately address concerns about effectiveness and rapidity of tear osmolarity measurement. It is well known that tear hyperosmolarity plays an important role in progression of inflammation and corneal epithelial damage in dry eye conditions by activating an inflammatory cascade.[41-43] Hence, change in tear osmolarity is an important underlying factor that, along with ocular inflammation, is responsible for symptoms of the disease.[43]

The main limitation of the present study was lack of any control group receiving artificial tears alone. In addition, although the participants were within the same age range and had a comparable time interval since exposure to MG, they were not completely homogeneous in terms of the frequency of different ocular abnormalities

such as limbal ischemia, corneal opacity and corneal vascularization at baseline. It may also be argued that concurrent administration of artificial tears with tCsA is responsible, at least in part, for the favorable effects that were observed in this study. However, it must be taken into account that all enrolled patients had been unresponsive to artificial tear treatment and sought additional medications. Therefore, it is less likely that improvement in signs and symptoms were related to the use of artificial tear.

Finally, it must be noted that although the efficacy measures in this study were significantly improved by tCsA, the effect size was generally small and thus may not be clinically significant. Nevertheless, it is plausible to obtain clinically relevant effects after longer durations of treatment.

In summary, our study showed that tCsA 0.05% is effective in reducing tear osmolarity as well as improving symptoms in patients suffering from MG-induced dry eye disease. Given the role of tear hyperosmolarity as a major determinant of the progression and severity of dry eye disease,[44] and a high frequency of chronic ocular complications in MG-exposed individuals, it is recommended that tCsA 0.05% be considered as a potential treatment for reduction of symptoms and improvement of quality of life. The interesting results of the present pilot study on the efficacy of tCsA in decreasing MG-induced dry eye symptoms generates the basis for conducting future large-scale randomized controlled trials.

ACKNOWLEDGEMENTS

The authors would also like to thank all the subjects who participated in this study. Mostafa Mafi wishes to thank the National Elite Foundation of Iran for its support. Results of this study have been partly presented in the ISOPT Clinical Congress (7–10 March 2013, Paris, France).

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How to cite this article: Jadidi K, Panahi Y, Ebrahimi A, Mafi M, Nejat F, Sahebkar A. Topical cyclosporine a for treatment of dry eye due to chronic mustard gas injury. J Ophthalmic Vis Res 2014;9:417-22.

Source of Support: Baqiyatallah University of Medical Sciences. **Conflict of Interest**: Baqiyatallah University of Medical Sciences.