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ORIGINAL ARTICLE

Efficacy of topical cyclosporine 0.5% in vernal keratoconjuctivitis.

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ABSTRACT… Objective: To evaluate the effectiveness of Topical cyclosporine 0.05% in comparison to topical artificial tear formulation (Tear Natural II) in the treatment of severe VKC. **Study Design:** Randomized Controlled Trial. **Setting:** Ziauddin University Hospital. **Period:** July 1 2022, to June 30, 2023. **Methods:** A group of individuals presented at the eye outpatient ophthalmology department (OPD) with complaints of redness, itching and watery discharges underwent clinical examination and were diagnosed with VKC based on inclusion criteria. Data was collected and analyzed using SPSS 23, with the Chi square test employed for variable comparisons. **Result:** In this study of 92 diagnosed VKC cases, participants were divided into two groups: Group 1 (interventional) and Group 2 (control), consisting of 47 and 38 individuals, respectively, with an average age of 9.6±2.3 years. Among them, 64 were boys (75.3%), and 21 were girls (24.7%). Group 1 showed improvement with a majority experiencing mild or quiescent symptoms, while Group 2 demonstrated worsening conditions, with a substantial portion reaching severe or very severe stages during the final follow-up assessment after six months. **Conclusion:** In conclusion, our research highlights the effectiveness of the topical cyclosporine o.o5% in significantly improving the condition of VKC patients over a six-month period.

Key words: Allergic Keratoconjunctivitis, Cyclosporine, Vernal Keratoconjuctivitis.

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a common type of allergic conjunctivitis, which causes inflammation of the conjunctiva due to an allergic reaction to substances such as pollen, dust mites, pet dander, or certain foods.[1] The prevalence of allergic conjunctivitis typically falls within the range of 6% to 30% and can vary depending on various factors, including geographic location, climate, genetics, and exposure to allergens.[2] Environmental factors, such as hot, dry, and dusty climates, play a significant role in the development and exacerbation of VKC. It often follows a seasonal pattern, with symptoms worsening during the spring and summer months.[3] VKC primarily affects children and young adults aged 5 to 15 years, with a higher incidence in males compared to females.[4] VKC represents an allergic reaction linked to the immunoglobulin (Ig) E-mediated release of histamine and other allergic reaction mediators from mast cells. Nevertheless, it's important to note that this is likely not the only mechanism contributing to the immunopathogenesis of VKC.[5] Studies have indicated that the inflammatory response seen in VKC also encompasses a T-helper (Th) type 2 hypersensitivity reactions, a late-phase allergic response characterized by eosinophil infiltration, and remodeling of the extracellular matrix.[6] There are multiple treatment options available, which include topical antihistamines, mast cell stabilizers, corticosteroids, and other therapies tailored to the individual's specific condition and needs.[7] Topical corticosteroids have been seen to be effective in reducing inflammation in recurrent and severe VKC. However, their long-term use is associated with various complications, including an increased risk of glaucoma and cataract.[8] Topical immunomodulators like cyclosporine and tacrolimus are commonly prescribed in cases of severe, recurrent VKC when corticosteroids are either ineffective or associated with undesirable

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side effects.[9] The key mechanism of action of cyclosporine in the treatment of VKC involves the inhibition of T-cell activation, the suppression of cytokine production, and the stabilization of mast cells, all of which collectively contribute to the reduction of inflammation in the eye.[10] The objective of our study is to evaluate the effectiveness of Topical cyclosporine 0.05% in comparison to topical artificial tear formulation (Tear Natural II) in the treatment of severe VKC. Our study offers evidence-based guidance to ophthalmologists, suggesting that topical immunomodulators should be considered as the treatment of choice for VKC, demonstrating improved outcomes with minimal to no side effects.

METHODS

A prospective randomized controlled trial was conducted at the Ophthalmology Department of Ziauddin Hospital in Karachi over the period of one year, spanning from July 1, 2022, to June 30, 2023. Ethical approval for the study was obtained following a thorough review by the institutional committee (2.6.22). The study focused on a group of pediatric patients who sought care at the Eye Outpatient Department (OPD). Inclusion criteria comprised children aged 7 to 14 years, diagnosed with severe VKC and those who had previously used topical steroids or mast cell stabilizers. Patients, included in this study, who were previously using other drugs for VKC treatment, were asked to stop all topical medications for a washout period of 1 month to fully wash out effects of the previous drugs.

The participants were evenly divided into two groups: an intervention group (Group-1) receiving Cyclosporine 0.05% and a control group (Group-2) receiving a placebo. Initially, there were 92 participants, with equal distribution between the two groups. However, approximately 7 patients were lost to follow-up, resulting in a final cohort of 85 participants for the study. Informed consent was obtained from all the parents and assent from patient before randomization. A questionnaire was filled out by a resident regarding patient demographics, presenting complaints, and clinical assessments during each follow-up visit. Following this, a single ophthalmologist conducted a thorough examination, including visual acuity testing and slit lamp examination on 1th, 3rd and 6th month.

We utilized the Bonini et al criteria, which are based on clinical characteristics, to grade the severity of VKC. Grade 0 is described as quiescent, indicating a state when the patient is free of symptoms. Papillae may be present, but there are no local signs of conjunctival hyperemia. Grade 1 (mild intermittent), patients had symptom during spring season, mild conjunctival hyperemia without corneal involvement and giant papillae may be present. Grade 2 (moderate intermittent/ persistent) symptoms and sign same as grade 1 but severity is increased. Grade 3 VKC is severe and presents with symptoms that persist on a daily basis, significantly impeding the patient's daily activities. This grade is characterized by pronounced conjunctival hyperemia, often accompanied by excessive eye secretions, the presence of Horner-Trantas dots, superficial punctate keratitis and Papillary reaction in Grade 3 VKC is typically moderate to severe. Grade 4 (very severe) if severe itching and photophobia are present everyday with mucus discharge on the ocular surface and between papillae, Horner-Trantas dots are present and corneal complications are common. The drug response was observed and documented on the basis of this criteria on every follow up visit.

The data were analyzed and entered into SPSS version 23. Quantitative variables, such as age, will be presented as mean ± standard deviation. Qualitative variables, like gender, will be presented as frequency and percentage. Comparative data will be analyzed using Chi- square test, with significance indicated by a p-value < 0.05.

RESULTS

This research included 92 diagnosed cases of VKC, which were subsequently divided into two groups: an interventional group (Group 1) and a control group (Group 2). Among the initial 92 patients, 7 were lost to follow-up, leaving 47 participants in Group 1 and 38 in Group 2. The average age of participants in both groups was

9.6±2.3 years. In terms of gender distribution, 64 participants were boys (75.3%), while 21 were girls (24.7%). These patients were using topical medication, with 51(60%) using topical steroids, 18(21.2%) using topical mast cell stabilizers, and 16 (18.8%) using topical antihistamines. These medications were previously being used by patients before participating in study, which were stopped for 1 month washout time. The patients were graded based on symptoms and clinical evaluation. The baseline evaluation showed 17 (20.0%) patients were in moderate condition, 50 (58.8%) were severe and 18 (21.2%) were very severe. After initiating treatment, a clinical assessment was conducted one month later to evaluate the response of patients in both group 1 and group 2. The results of this assessment indicate a favorable response to treatment in group 1 as compare to group 2. (Table-I) After one month of evaluation, the results showed that in Group 1, 10 (21.3%) patients had mild intermittent symptoms, 19 (40.4%) had moderate symptoms, 14(29.8%) had severe symptoms, and 4(8.5%) were evaluated as very severe. In the evaluation of Group 2, 2 patients exhibited mild symptoms, 10 had moderate symptoms, 19 experienced severe symptoms, and 7 were assessed as having very severe symptoms. In the second follow-up at the third month, the results indicated improvement. Among the patients in Group 1, 5 (10.6%) were classified as having mild symptoms, 26 (55.3%) as moderate, 8 (17.1%) as severe, 5 (10.6%) as very severe, and 3 (6.4%) as extremely severe.

During the third-month evaluation, Group 2 was assessed, revealing that 5 patients (13.2%) had mild symptoms, 13 (34.2%) had moderate symptoms, 16 (42.1%) had severe symptoms, and 4 (10.5%) were classified as very severe.

At the final follow-up in the sixth month, the assessment for Group 1 revealed that 17 patients (36.2%) were classified as being in a quiescent stage, 24 (51.0%) had mild symptoms, and 6 (12.8%) had moderate symptoms. In contrast, the evaluation for Group 2 showed worsened conditions, with 15 patients (39.5%) at a moderate stage, 17 (44.7%) at a severe stage, and 6 (15.8%) at a very severe stage.

Clinical Grading	Group 1	Group 2
Grade 1 (mid intermittent)	10 (21.3%)	2 (5.3%)
Grade2 (moderate intermittent/ persistent)	19 (40.4%)	10 (26.3%)
Grade 3 (severe)	14 (29.8%)	19 (50%)
Grade 4 (very severe)	4 (8.5%)	7 (18.4%)

Table-I. 1st follow up (1st month) clinical evaluation

The chi-square statistic is 8.84. The p-value is 0.031.The result is significant at $p < .05$.

	Group 1	Group 2
GRADE 0 (Quiescent)	5(10.6%)	0 (0%)
GRADE1 (mid intermittent)	26 (55.3%)	5 (13.2%)
GRADE 2 (moderate intermittent/ persistent)	8 (17.1%)	13 (34.2%)
GRADE 3 (Severe)	5 (10.6%)	16 (42.1%)
GRADE 4 (Very Severe)	3 (6.4%)	4 (10.5%)

Table-II. 2nd follow up (3rd month) clinical evaluation

The chi-square statistic is 23.4464. The p-value is .000103. The result is significant at $p < .05$.

	Group 1	Group 2
Grade 0 (Quiescent)	17 (36.2%)	0 (0%)
Grade 1 (mid intermittent)	24 (51.0%)	0 (0%)
Grade 2 (moderate intermittent/ persistent)	6 (12.8%)	15 (39.5%)
Grade 3 (Severe)	0 (0%)	17 (44.7%)
Grade 4 (Very Severe)	0 (0%)	6 (15,8%)

Table-III. 3rd follow up (6th month) clinical evaluation

The chi-square statistic is 55.123. The p-value is .00001. The result is significant at $p < .05$.

DISCUSSION

Vernal keratoconjunctivitis (VKC) is a type of allergic conjunctivitis, and its symptoms typically begin to resolve spontaneously around the time of puberty.[11,12] Its management involves a combination of strategies, incorporating medical intervention and preventive measures aimed at symptom control and complication prevention.[13,14] It's important to emphasize that there is no universally recommended treatment for VKC, and treatment plans may differ depending on the condition's severity and individual patient characteristics.[15,16] The initial step in addressing VKC is the identification and avoidance of allergens responsible for triggering the condition. These allergens commonly include substances such as pollen, dust mites, and animal dander. Topical steroids are the most effective treatment

for severe VKC, as they suppress inflammatory pathways and inhibit phagocytic responses.[17,18] However, prolonged use of topical steroids can lead to serious adverse effects, including glaucoma, cataract and corneal ulcer. Due to these significant side effects, long-term use of steroids is not recommended for VKC.[19,20] Instead, other treatment options such as topical mast cell stabilizers, topical antihistamines, and non-steroidal anti-inflammatory agents can be considered for managing mild to moderate VKC.[21,22,23] These alternatives, however, are effective in mild to moderate cases of the disease. Cyclosporine-A is an immunosuppressive agent that not only inhibits the multiplication of Th-4 lymphocytes and the formation of IL-2 but also effectively addresses severe cases, all while causing minimal side effects. Numerous studies have documented the efficacy of topical Cyclosporine-A therapy in VKC.[24,25]

Ahmed A and colleagues conducted a study in which they analyzed the efficacy of cyclosporine in cases that did not respond to antihistamines and mast cell stabilizers. Clinical assessments were conducted at the beginning of the study and at the 1st, 2nd, and 4th month after commencing therapy. Following four months of topical treatment, patients not only experienced symptomatic improvement but also showed significant improvement in their clinical signs.[26]

In the study conducted by Chatterjee A et all, Indian researchers analyzed the Efficacy, Safety, and Steroid-sparing Effect of Topical Cyclosporine A 0.05% for Vernal Keratoconjunctivitis. The Cs A group consistently demonstrated a significantly greater reduction in both symptom scores ($P < 0.0001$ in all follow-up visits) and sign scores ($P < 0.0001$ in all follow-up visits) compared to the placebo group.[27]

The mean age of the patients in Nirmala Met all study was 16.56 years, and the average duration of VKC was 8.4 years. After treatment with cyclosporine eye drops, the patients were monitored for an average duration of 10 months, with a range between 6 to 12 months. All symptoms, including itching, redness, photosensitivity, foreign body sensation, and mucus discharge, improved following the treatment. Furthermore, there was an improvement in objective signs such as conjunctival hyperemia, conjunctival papillary hypertrophy, giant papillae, limbal hypertrophy, corneal punctate epithelial erosions, and corneal pannus.[28]

In the research conducted by Ganjoo S and their team, they conducted a comparative analysis between loteprednol etabonate 0.5% and cyclosporin-A 0.05% as treatments for VKC. Their findings indicate that loteprednol etabonate and cyclosporin-A 0.05% were equally effective in severe VKC.[29]

The study conducted by Bremond-GD et all found significant improvement in signs and symptoms in pediatric patients with severe VKC when using Cyclosporine A cationic emulsion (CsA CE) 0.1% eye drops. These findings suggest that CsA CE may be an effective treatment option for VKC in pediatric patients.[30] In our study, we assess the efficacy of cyclosporine in the treatment of severe and chronic cases of VKC.

We noted a substantial improvement in both the clinical signs and the subjective symptoms experienced by the patients who received cyclosporine treatment as compare to the control group. VKC is a chronic and often severe form of allergic conjunctivitis, particularly common in children, which can lead to severe discomfort, visual disturbances, and a considerable burden on patients and their families. These findings suggest that cyclosporine may be a valuable therapeutic option for managing severe and chronic cases of VKC, offering hope for patients and their families.

This study highlights the significance of exploring innovative therapeutic approaches and interventions to elevate the overall quality of life for individuals afflicted by VKC. Furthermore, it makes a valuable contribution to the expanding the collection of knowledge focused on enhancing the management of this intricate eye ailment.

CONCLUSION

In our study, the use of topical Cyclosporine 0.05% has demonstrated its effectiveness in treating vernal keratoconjunctivitis (VKC). It successfully relieved the signs and symptoms of VKC, all while presenting minimal side effects. The introduction of a user-friendly, low-dosage regimen contributed to enhanced patient compliance and significantly elevated their quality of life.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Amber Khalid	Concept, design, and main contributor in writing the manuscript. Patient selection and Interpretation of data.	
2	Kanwal Zehra Rizvi	Edited and contributed in writing the manuscript, Interpretation of data.	
3	Quratulain	Reference and proof read the article.	
4	Aveen Fatima	Literature researchc for disussion and references.