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To study efficacy of tacrolimus (0.03%) eye ointment, cyclosporine (0.1%) eye drops and fluorometholone (0.1%) eye drops in vernal keratoconjunctivitis

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ABSTRACT

Background: VKC (Vernal keratoconjunctivitis) is a chronic, bilateral ocular inflammatory disorder that primarily impacts young patients. Management of VKC is challenging due to its complex immunological etiology and chronic inflammatory components.

Materials and Methods: This prospective, single-center, randomized study was executed at the Outpatient Department of Ophthalmology, SGT Medical College, Hospital and Research Institute (FMHS), Budhera, Gurugram, for a duration of 18 months. A total of 102 clinically diagnosed VKC patients, aged above 5 years, have been then randomly divided into 3 groups (34 each). Group A received fluorometholone (0.1%) eye drops, Group B received cyclosporine (0.1%) eye drops, and Group C received tacrolimus (0.03%) eye ointment. Patients were evaluated at days 0, 7, 14, 28, 35, and two weeks post-medication using the Clinical Scoring System by Bleik and Tabbara to assess TSSS (Total Subjective Symptom Score) and TOSS (Total Objective Ocular Sign Score).

Results: Most patients were between 6-10 years old, with over 78% being males. Group A showed significant symptom reduction from the first week (mean TSSS reduction from 2.29±0.46 to 0.21±0.41, $p<0.0001$), while Groups B and C showed significant improvements from the second week (Group B: mean TSSS reduction from 2.5±0.51 to 0.12±0.33, $p<0.0001$; Group C: mean TSSS reduction from 2.29±0.46 to 1.00±0.00, $p<0.0001$). Conjunctival hyperemia and tarsal papillae improvements were more pronounced in Group B as compared to Groups A & C. No ocular complications were found, except for dose-dependent irritation in Group C.

Conclusion: While fluorometholone (0.1%) eye drops provided early symptom relief, its effects were not sustained. Cyclosporine (0.1%) eye drops and tacrolimus (0.03%) eye ointment showed delayed but sustained efficacy, making them suitable for long-term treatment of moderate to severe VKC. Fluorometholone may be used initially alongside immunomodulators for rapid symptom relief, followed by tapering as immunomodulators take effect.

1. Introduction

VKC is a chronic, bilateral, external ocular inflammatory condition that predominantly impacts individuals in their 1^{st} & 2^{nd} decade of life.[1] VKC comprises two phases: acute and late. During the acute phase, patients exhibit pruritus, lacrimation, erythema, photophobia, eyelid edema, and conjunctival chemosis. This phase is mediated by mast cells. In the advanced stage, severe symptoms, including visual impairment from corneal scarring and limbal cell

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deficiency, manifest, demonstrating a typical late-phase reaction linked to eosinophilia and neutrophilia.[2] VKC differs from seasonal/perennial allergic conjunctivitis and other forms of allergic conjunctivitis as it is mediated by T-helper 2 lymphocytes.[3] The specific functions of eosinophils, mast cells, cytokines, and fibroblasts in inflammation and conjunctival tissue remodeling remain inadequately defined.[4]

The symptoms of VKC encompass itching, a burning sensation, excessive tearing, a sensation of a foreign body, photophobia, and mucous discharge. Management of VKC includes supportive treatments such as the use of sunglasses outdoors, avoiding known allergens, and applying cold compresses.[5] Commonly used pharmacological agents include vasoconstrictor/antihistaminic combination topical agents like naphazoline and pheniramine, antihistamines such as levocabastine and emedastine, mast cell stabilizers involving sodium nedocromil, cromoglycate, and iodoxamide, topical steroids like loteprednol, fluorometholone, and desonide, and immunomodulators such as cyclosporine and tacrolimus.[6]

VKC exhibits clinical characteristics and pathogenic mechanisms akin to other types of allergic conjunctivitis, including ocular pruritus, edema, erythema, and conjunctival papillary response linked to IgE-mediated histamine release from mast cells.[7] Nonetheless, merely 50% of VKC cases exhibit allergic sensitization, suggesting that the inflammatory response in VKC also encompasses a Th2-mediated late-phase allergic reaction characterized by eosinophil infiltration along with extracellular matrix remodelling.[8–10]

This research aims to analyze and compare the efficacy of tacrolimus (0.03%) eye ointment, cyclosporine (0.1%) eye drops, and fluorometholone (0.1%) eye drops in managing VKC, given the limited literature on their comparative effectiveness.

2. Materials and Methods

2.1. Study design and methodology

This research was structured as a prospective, "single-center, randomized trial carried out at the Outpatient Department of Ophthalmology at SGT Medical College, Hospital and Research Institute (FMHS), Budhera, Gurugram". The research duration was 18 months, and inclusion criteria included clinically diagnosed cases of VKC and patients older than 5 years of age. Exclusion criteria included patients younger than 5 years, as well as pregnant and lactating women, patients on other topical drug therapies or steroidal therapy, those with ocular infections, contact lens wearers, and patients with any ocular pathology or surgery within the last 6 months.

Informed and written consent was obtained from all participants. Data collection involved a piloted proforma through personal interviews with patients who met the inclusion criteria. A detailed clinical history was recorded, including the duration of complaints, aggravating and relieving factors, and past treatment history. Visual acuity was assessed using Snellen's chart, followed by a thorough clinical examination under torchlight and slit lamp, focusing on the tarsal and bulbar conjunctiva, palpebral conjunctiva, limbus, and cornea. Key examination parameters included the presence and size of papillae, conjunctival hyperemia, chemosis, scarring, perilimbal congestion, gelatinous thickening, Tranta spots, superficial epithelial keratitis, epithelial erosions, and shield ulcers. Symptoms and signs were graded on a scale from 0 to 3 using "the Clinical Scoring System by Bleik and Tabbara.

Patients were" divided into three groups using MS Excel's RAND between function. Group A received fluorometholone (0.1%) eye drops, tapered over four weeks with scheduled follow-ups at days 0, 7, 14, 28, 35, and two weeks post-medication. Group B was treated by using cyclosporine (0.1%) eye drops applied four times daily for four weeks with similar follow-up schedules. Group C applied tacrolimus (0.03%) eye ointment 2X daily for four weeks, followed by the same follow-up intervals. Clinical data were recorded in a structured proforma, and the TSSS and TOSS were evaluated before & after each visit. Statistical analysis was conducted to compare the efficacy of the treatments, with significance levels set "at $p<0.05$, very significant at $p<0.01$, and highly significant at $p<0.001$.

3. Results

3.1. Age and sex distribution

The age distribution of patients in the study indicated that the predominant age group was 6-10 years: 50.00% in Group A, 44.12% in Group B, and 47.06% in Group C. The average ages were 8.64±3.15 years for Group A, 9.35±3.03 years for Group B, and 8.79±3.06 years for Group C. No statistically significant variations have been observed between the groups (Group A v/s Group B, p=0.350; Group A v/s Group C, p=0.845; Group B v/s Group C, p=0.755). Males were predominant in all groups, comprising 79.41% in Group A, 85.29% in Group B, and 79.41% in Group C, with no statistically significant difference (chi-square = 0.517, p = 0.772).

3.2. Total subjective symptom score (TSSS) and total objective ocular sign score (TOSS)

The TSSS" showed significant improvement in all groups over time (Table 1). In Group A, the mean TSSS reduced from 2.29±0.46 at baseline to 0.21±0.41 at day 35, and further to 0.15±0.36 two weeks after stopping the medication ($p<0.0001$). In Group B, the mean TSSS reduced from 2.5±0.51 at baseline to 0.12±0.33 at day

Table 1: Changes in TSSS and TOSSduring follow-up visits

"Time	Group A TSSS Mean±SD	Group B TSSS Mean±SD	Group C TSSS Mean±SD	Group A TOSS Mean±SD	Group B TOSS Mean±SD	Group C TOSS Mean±SD "
0 Day	2.29±0.46	2.5±0.51	2.29±0.46	4.44±1.33	5.65±1.1	5.15±1.69
7 Days	2.06±0.42	2.00±0.00	2.29±0.46	3.82±1.22	4.88±0.95	5.24±1.72
14 Days	1.53±0.51	1.53±0.51	1.85±0.36	2.41±1.08	3.82±1.24	3.71±1.03
28 Days	0.85±0.5	1.09±0.29	1.29±0.46	1.21±0.91	3.29±0.87	2.88±0.73
35 Days	0.21±0.41	0.12±0.33	1.00±0.00	0.32±0.68	0.00±0.00	0.74±0.57
2 weeks w/o med	0.15±0.36	0.06±0.24	0.09±0.29	0.21±0.54	0.06±0.24	0.18±0.58

Table 2: Mean reduction in symptoms and signs at every visit

Variables	Day 0 Mean±SD	Day 7 Mean±SD	Day 14 Mean±SD	Day 28 Mean±SD	Day 35 Mean±SD	2 Weeks Without Medication Mean±SD
Group A						
Symptom	2.29±0.46	2.12±0.33	1.53±0.51	0.85±0.5	0.21±0.41	0.12±0.33
Conjunctival Hyperemia	1.76±0.55	1.59±0.5	0.88±0.41	0.65±0.49	0.18±0.39	0.09±0.29
Papillae	1.53±0.51	1.21±0.41	0.85±0.5	0.32±0.47	0.06±0.24	0.12±0.33
Tranta's Dots	0.91±0.67	0.88±0.64	0.56±0.56	0.21±0.41	0.00±0.00	0.00±0.00
Limbal Infiltration	0.18±0.46	0.24±0.5	0.09±0.29	0.00±0.00	0.03±0.17	0.00±0.00
Group B						
Symptom	2.5±0.51	2.00±0.00	1.53±0.51	1.09±0.29	0.12±0.33	0.06±0.24
Conjunctival Hyperemia	2.00±0.00	2.00±0.00	1.53±0.51	1.12±0.33	0.00±0.00	0.06±0.24
Papillae	2.00±0.00	1.59±0.5	1.09±0.29	1.00±0.00	0.00±0.00	0.00±0.00
Tranta's Dots	1.24±0.7	0.82±0.46	0.79±0.41	0.79±0.41	0.00±0.00	0.00±0.00
Limbal Infiltration	0.44±0.5	0.44±0.5	0.41±0.5	0.38±0.49	0.00±0.00	0.00±0.00
Group C						
Symptom	2.29±0.46	2.29±0.46	1.85±0.36	1.29±0.46	1.00±0.00	0.09±0.29
Conjunctival Hyperemia	2.03±0.52	2.03±0.52	1.47±0.51	1.15±0.36	0.62±0.49	0.09±0.29
Papillae	1.59±0.56	1.65±0.6	1.18±0.39	1.03±0.17	0.18±0.39	0.09±0.29
Tranta's Dots	1.15±0.66	1.18±0.67	0.82±0.39	0.71±0.46	0.00±0.00	0.00±0.00
Limbal Infiltration	0.38±0.55	0.38±0.55	0.24±0.43	0.00±0.00	0.00±0.00	0.00±0.00

35, and further to 0.06±0.24 two weeks after stopping the medication (p<0.0001). Group C depicted a decrease from 2.29±0.46 at baseline to 1.00±0.00 at day 35 and to 0.09±0.29 two weeks after stopping the medication (p<0.0001). The mean reduction in TSSS at different follow-up visits showed significant differences between the groups, with Group B and Group C showing better sustained improvements compared to Group A (p<0.05).

The TOSS also improved significantly in all groups (Table 1). In Group A, the mean TOSS decreased from 4.44±1.33 at baseline to 0.32±0.68 at day 35, and to 0.21±0.54 two weeks after stopping the medication (p<0.0001). In Group B, the mean TOSS decreased from 5.65±1.1 at baseline to 0.00±0.00 at day 35, and to 0.06±0.24 two weeks after stopping the medication (p<0.0001). Group C depicted a decrease from 5.15±1.69 at baseline to 0.74±0.57 at day 35 and to 0.18±0.58 two weeks after stopping the medication (p<0.0001). The mean reduction in TOSS at different follow-up visits showed significant differences between the groups, with Group B demonstrating the most pronounced and sustained improvement (p<0.05).

3.3. Overall symptom and sign reduction

The mean reduction in symptoms and various signs was notable across all groups (Table 2). In Group A, significant reductions were observed in symptoms, conjunctival hyperemia, and papillae over the study period. Group B showed similar improvements, with a notable reduction in tranta's dots and limbal infiltration. Group C also demonstrated significant reductions in symptoms, conjunctival hyperemia, and papillae, though it initially

showed an increase in papillae size before a subsequent decrease. Overall, Group A showed the fastest initial symptomatic relief but had less sustained effects compared to Groups B and C, which had slower initial improvements but more sustained relief from symptoms and signs of VKC

4. Discussion

In this study, 102 patients "were recruited and evenly allocated into three groups of 34 individuals each. Group A received Fluorometholone 0.1% eye drops. Significant improvement was observed after one week, consistent with previous studies evaluating the efficacy of Fluorometholone in VKC.[11,12] Fluorometholone showed a rapid onset of action, providing early relief, but its effects were not sustained throughout the study period. This aligns with the findings of Bonini et al. (1999), who compared the effectiveness of topical nedocromil 2% with Fluorometholone 0.1% and found that Fluorometholone provided a significant reduction in VKC signs and symptoms than to nedocromil.[13]

Group B was treated with Cyclosporine 0.1% eye drops". Clinical response was evident from the second week of treatment, with maximum improvement observed in four weeks and sustained effects. This is consistent with the research by Ebihara et al. (Japan), which found Cyclosporine 0.1% effective in treating VKC, with improvement in symptoms and minimal recurrence after stopping therapy.[14] Cyclosporine, being an immunomodulator, takes time to act but provides sustained effects, reducing the percentage of patients experiencing recurrence compared to Group A.

Group C had been then treated with Tacrolimus 0.03% eye ointment. Clinical response was evident from the second week, reaching maximum efficacy in four weeks with sustained effects. However, patients experienced an initial stinging sensation, affecting compliance and follow-up. A study by Rashmi Kumari et al. in Nepal comparing the efficacy of 0.03% Tacrolimus and 0.05% Cyclosporine found consistent reductions in TSSS & TOSS in both groups without apparent adverse impacts, which aligns with the current study's findings.[15]

5. Conclusion

In conclusion, while fluorometholone 0.1% eye drops provided early and marked relief, its effects were not lasting. Cyclosporine 0.1% eye drops and Tacrolimus 0.03% ointment of eye had delayed onset but sustained effects, making them better suited for moderate to severe VKC cases requiring prolonged treatment. Fluorometholone 0.1% may be used in the early phase along with immunomodulators for early relief, then tapered off as the immunomodulators take effect.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

1. Tabbara KF, Aref GH, Kharashi SA, Mansouri SM. Vernal keratoconjunctivitis in Saudi Arabia. *Doc Ophthalmol*. 1999;98(1):23–8.
2. Leonardi A. Management of vernal keratoconjunctivitis. *Ophthalmol Ther*. 2013;2(2):73–88.
3. Sacchetti M, Plateroti R, Bruscolini A, Giustolisi R, Marenco M. Understanding Vernal Keratoconjunctivitis: Beyond Allergic Mechanisms. *Life (Basel)*. 2021;26(10):1012.
4. Ramirez GA, Yacoub MR, Ripa M, Mannina D, Cariddi A. Eosinophils from Physiology to Disease: A Comprehensive Review. *Biomed Res Int*. 2018;28:9095275–9095275.
5. Mehta JS, Chen WL, Cheng ACK, Cung LX, Dualan IJ. Diagnosis, Management, and Treatment of Vernal Keratoconjunctivitis in Asia: Recommendations From the Management of Vernal Keratoconjunctivitis in Asia Expert Working Group. *Front Med (Lausanne)*. 2022;9:882240.
6. Hehar NK, Chigbu DI. Vernal Keratoconjunctivitis: Immunopathological Insights and Therapeutic Applications of Immunomodulators. *Life (Basel)*. 2024;14(3):361.
7. Villegas BV, Benitez-Del-Castillo JM. Current Knowledge in Allergic Conjunctivitis. *Turk J Ophthalmol*. 2021;51:45–54.
8. Leonardi A. Vernal keratoconjunctivitis: pathogenesis and treatment. *Prog Retin Eye Res*. 2002;2(3):319–39.
9. Bonini S, Bonini S, Lambiase A, Marchi S, Pasqualetti P, Zuccaro O, et al. Vernal keratoconjunctivitis revisited. A case series of 195 patients with long-term followup. *Ophthalmology*. 2000;107(6):1157–63.
10. Mantelli F, Santos MS, Petitti T, Sgrulletta R, Cortes M, Bonini S. Systematic review and meta-analysis of randomized clinical trials on topical treatments for vernal keratoconjunctivitis. *Br J Ophthalmol*. 2007;91(12):1656–61.
11. Roumeau I, Coutu A, Navel V, Pereira B, Baker JS. Efficacy of medical treatments for vernal keratoconjunctivitis: A systematic review and meta-analysis. *J Allergy Clin Immunol*. 2021;148(3):822–34.
12. Öner V, Türkcü FM, Taş M, Alakuş MF, Işcan Y. Topical loteprednol etabonate 0.5 % for treatment of vernal keratoconjunctivitis: efficacy and safety. *Jpn J Ophthalmol*. 2012;56(4):312–8.
13. Bonini S, Coassin M, Aronni S, Lambiase A. Vernal keratoconjunctivitis. *Eye (Lond)*. 2004;18:345–51.
14. Ebihara N, Ohashi Y, Uchio E, Okamoto S, Kumagai N, Shoji J. A large-scale epidemiological study of Japanese patients with vernal keratoconjunctivitis. *Jpn J Ophthalmol*. 2010;54:343–7.
15. Kumari R, Saxena S, Gautam S, Upadhyay N, Singh S. Comparative study of 0.03% tacrolimus ointment versus 0.05% cyclosporine A eye drops in vernal keratoconjunctivitis. *Nepal J Ophthalmol*. 2014;6:229–35.

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