ORIGINAL RESEARCH

A comparative study of Rebamipide, Cyclosporine, and Olopatadine in the treatment of Vernal Keratoconjunctivitis in the rural population of Central India

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ABSTRACT

Introduction: Vernal keratoconjunctivitis (VKC) is a chronic bilateral allergic eye disease affecting children, causing significant morbidity. Despite its prevalence, there is no permanent cure, and severe cases pose management challenges. This study aimed to compare the efficacy of Rebamipide, Cyclosporine, and Olopatadine in treating severe VKC, assessing complications and relapse rates. **Methods:** A 16-month prospective study enrolled 270 VKC patients aged 4-20 years. Patients were randomized into three groups receiving Rebamipide, Cyclosporine, or Olopatadine. Standardized assessments were conducted at weeks 0, 2, 6, and 12, including clinical examinations and Bleik scoring. Statistical analysis employed ANOVA, Tukey's post-hoc tests, and paired t-tests. **Results:** Significant age differences were observed among groups, with males predominantly affected. All treatments demonstrated efficacy, with Rebamipide showing consistent improvement in total subjective symptom scores (TSSS) and total objective ocular sign scores (TOSS) over 12 weeks. Complication rates were low. **Conclusion:** Rebamipide, Cyclosporine, and Olopatadine exhibited similar efficacy and safety profiles in treating severe VKC. Treatment, along with artificial tear and soft steroid, significantly reduced clinical symptoms and signs without serious adverse effects. Further multicentric studies are warranted for conclusive determination of drug regimen superiority. This research contributes valuable insights into managing VKC, especially in regions like northern India grappling with its increasing burden.

Keywords: Vernal keratoconjunctivitis, Allergic eye disease, Rebamipide, Cyclosporine, Olopatadine, Bleik scoring

INTRODUCTION

Vernal keratoconjunctivitis (VKC) stands as a prevalent, chronic, and severe bilateral allergic eye disease, primarily affecting children and adolescents with seasonal recurrence. Its symptoms, such as hyperaemia, itching, tearing, photophobia, and mucous discharge, pose significant challenges, especially in engaging children in normal activities. VKC is marked by cobblestone papillae, papillary hypertrophy on the limbal conjunctiva, Horner-Tranta's dots, corneal erosions, and shield ulcers. These symptoms can lead to giant papillae, causing discomfort and impairment.[1]

Typically, VKC manifests in the first decade of life, with symptoms disappearing during the second decade. It can have mild or severe chronic forms, potentially causing permanent changes like scarring, keratoconus, and corneal shield ulcers, leading to visual impairment.[2]

VKC is characterized by both IgE- and cell-mediated immune mechanisms and primarily affects boys, with onset usually around the age of five. The disease

exhibits racial and geographical variations, being more common and severe in hot, arid regions like the Mediterranean basin, West Africa, and the Indian subcontinent. In temperate regions, VKC is rare, but when present, it often coexists with other atopic conditions such as asthma and eczema.The diagnosis is based on classical symptoms of conjunctivitis and specific ocular signs, including cobblestone papillae and Trantas dots. Corneal involvement, known as vernal keratopathy, is associated with more severe disease.[3]

VKC not only impacts physical health but also affects the daily lives and social interactions of children. It can limit activities causing exposure to allergens or irritants, such as playing outdoors or going to the pool.The north of India, particularly Uttar Pradesh, grapples with a rising burden of VKC, affecting young school-going children and distracting them from their education and growth. The prolonged natural course of the disease, lasting 4 to 10 years, steals precious years of productivity from the working population. Uttar Pradesh University of Medical Sciences Saifai witnesses a considerable influx of patients with varying degrees of VKC every year.[4]

Despite advancements in understanding and treatment, there is no permanent cure for VKC. Treatment options focus on temporarily controlling inflammation, including the use of topical steroids, mast cell stabilizers, topical NSAIDs, immunotherapeutic agents, and ganglioside derivatives. Unfortunately, severe refractory VKC often proves challenging to manage with these modalities.[5]

AIM AND OBJECTIVES

1. To compare the efficacy of Rebamipide [2% w/v] eye drops, Cyclosporine 0.05% eye drops, and Olopatadine [0.1%] eye drops in the treatment of severe vernal keratoconjunctivitis.
2. To evaluate the complication and relapse rates among users of the three drugs.

MATERIAL AND METHODS

This prospective, randomized, double-masked comparative study was conducted at the Ophthalmology department of Uttar Pradesh University of Medical Sciences Saifai over 16 months, from November 2018 to March 2020, with a 3-month follow-up. The study included 270 patients (510 eyes) diagnosed with severe vernal keratoconjunctivitis (VKC) and aimed to assess the efficacy of three eye drops: Rebamipide [2% w/v], Cyclosporine 0.05%, and Olopatadine [0.1%].

Patients were divided into three groups based on the type of eye drops: Group-A (Rebamipide), Group-B (Cyclosporine), and Group-C (Olopatadine). Standardized assessments were performed using Snellen's distance visual acuity chart, a ZEISS Slit lamp with a 90 Diopter lens, and a TONOPEN REICHERT tonometer.

The study protocol involved four visits at weeks 0, 2, 6, and 12. Patients underwent a comprehensive examination, including general, physical, and ophthalmologic assessments. The diagnosis of VKC was confirmed clinically, and the severity of signs and symptoms was graded using the Bleik scoring system.

The primary objective was to compare the efficacy of Rebamipide, Cyclosporine, and Olopatadine in treating severe VKC. Secondary objectives included evaluating complication and relapse rates among the three drug groups. Adverse reactions, such as ocular discomforts, were assessed within 30 minutes after medication administration.

Inclusion criteria comprised patients with symptoms and signs confirming VKC diagnosis, aged 4-20 years, and willing to participate through informed consent. Exclusion criteria included coexisting ocular/systemic diseases, previous ocular surgery, single-eyed patients, pregnancy/lactation, contact lens wearers, known allergy to eye drop components, continued use of eye drops, punctal plug within 3 months, enrollment in other studies, and unwillingness to participate.

The grading system included Bleik scores for symptoms (itching, tearing, photophobia, discharge, foreign body sensation) and signs (conjunctival hyperemia, palpebral conjunctival papillae, punctate keratitis, Trantas dots, limbal infiltration). The study outcomes were measured in terms of total subjective symptom scores (TSSS) and total objective ocular sign scores (TOSS) before and after treatment at each visit.

STATISTICAL ANALYSIS

The results are presented in frequencies, percentage and mean±SD. The Chi-square test was used to compare categorical variables. The one-way analysis of variance (ANOVA) followed by Tukey's post-hoc tests to compare continuous variables among the groups at all the time periods. The Paired t-test was used to compare mean change in continuous variables. The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

RESULTS

The present study was conducted in the Department of Ophthalmology, UPUMS Saifai with the objective to compare the efficacy of Rebamipide [2% w/v] eye drop, cyclosporine 0.05% E/D and Olopatadine [0.1%] E/D in the treatment of severe Vernal Keratoconjunctivitis. The sample size was 270. A total of 90 patients in each group were included in the study.

Group A: Patient receiving **Rebamipide**eye drops.
Group B: Patient receiving **Cyclosporine** eye drops.
Group C: Patient receiving **Olopatadine** eye drops.

Table-1: Distribution of age among the groups

Groups	Age in years (Mean±SD)
Group A	13.64±4.45
Group B	11.84±4.29
Group C	8.69±4.33
p-value[1]	0.0001*
p-value[2]	
Group A vs Group B	0.01*
Group A vs Group C	0.0001*
Group B vs Group C	0.0001*

[1]ANOVA test, [2]Post-hoc tests, *Significant

Table-1 & Fig.1 shows the distribution of age among the groups. The mean age of patients of Group A, Group B and Group C were 13.64±4.45, 11.84±4.29 and 8.69±4.33 years respectively. The analysis of variance revealed that there was significant (p=0.0001) difference in age among the groups. The post-hoc tests showed that age was significantly (p<0.05) different between each pair of groups.

AGE: - There was a significance difference in the mean age among Group A, Group B and Group C. The maximum number of patient in group A group B, Group C with mean age was 13.64±4.45, 11.84±4.29 and 8.69±4.33 years respectively. The analysis of variance revealed that different between age was significant with P value <0.05 in each pair of groups

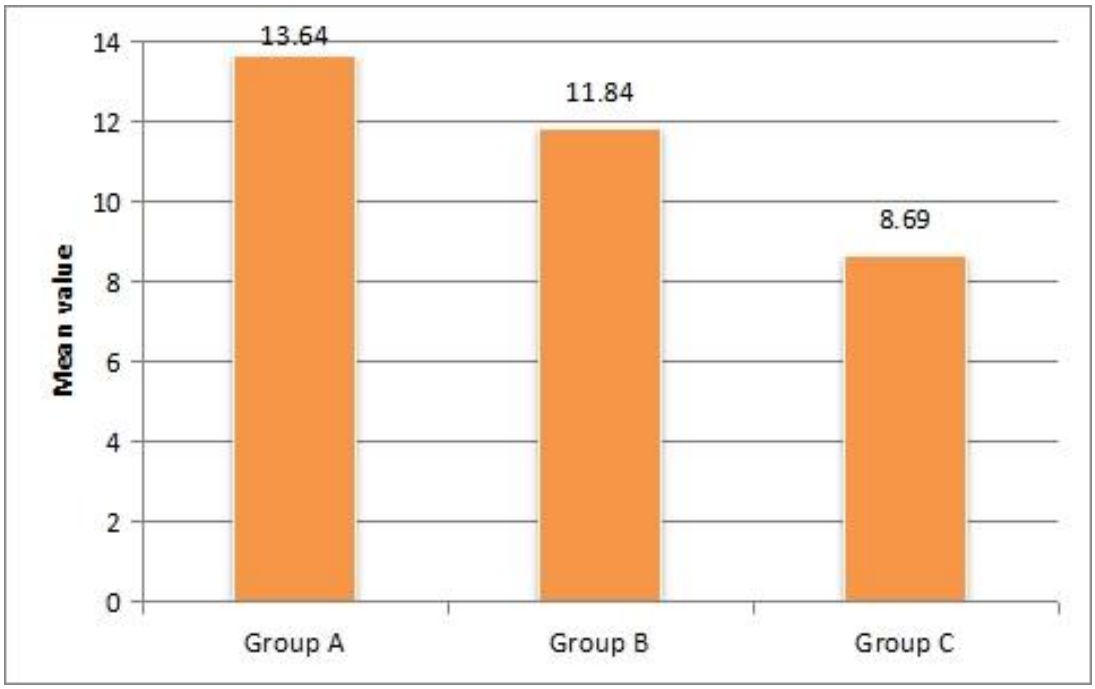

Fig. 1: Distribution of age among the groups

Table-2: Distribution of gender among the groups

Gender	Group A (n=90)		Group B (n=90)		Group C (n=90)		p-value[1]
	No.	%	No.	%	No.	%	
Male	66	73.3	72	80.0	73	81.1	0.39
Female	24	26.7	18	20.0	17	18.9	

[1]Chi-square test

Table-2 & Fig.2 shows the distribution of gender among the groups. Majority of patients in all Group A (73.3%), Group B (80%) and Group C (81.1%) were males. There was no significant (p>0.05) difference in gender among the groups.

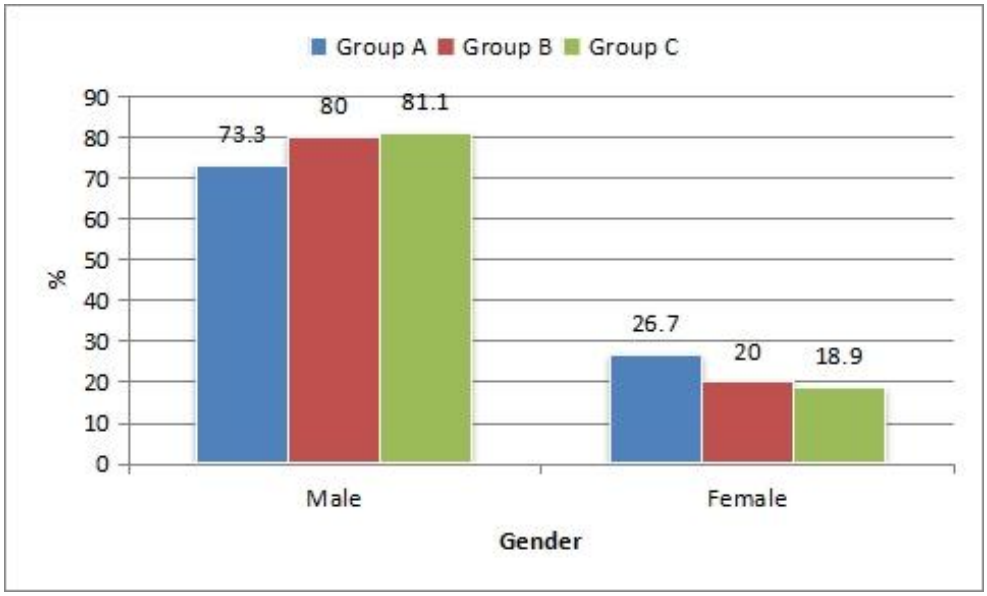

Fig. 2: Distribution of gender among the groups

Table-3: Comparison of TSSS among the groups across the time periods

Groups	Group A (n=90)	Group B (n=90)	Group C (n=90)	p-value[1]	p-value[2]		
					Group A vs Group B	Group A vs Group C	Group B vs Group C
At entry	11.07±0.68	10.70±1.11	10.39±1.37	0.0001*	0.06	0.0001*	0.13
2 weeks	8.01±1.20	7.26±1.02	6.76±1.44	0.0001*	0.0001*	0.0001*	0.01*
6 weeks	5.53±1.38	4.19±1.17	3.94±1.11	0.0001*	0.0001*	0.0001*	0.37
12 weeks	3.86±0.66	2.02±0.56	2.22±0.53	0.0001*	0.0001*	0.0001*	0.06

[1]ANOVA test, [2]Post-hoc tests, *Significant

Table-3 & Fig.3 shows the comparison of TSSS among the groups across the time periods. The analysis of variance revealed that there was significant (p=0.0001) difference in TSSS among the groups at all the time periods. The post-hoc tests showed that TSSS was significantly (p=0.0001) different between Group A and Group C at entry. There was significant (p=0.0001) difference in TSSS between each pair of groups at 2 weeks. TSSS was significantly (p=0.0001) different between Group A & Group B and Group A & Group C at 2 weeks, 6 weeks and 12 weeks.

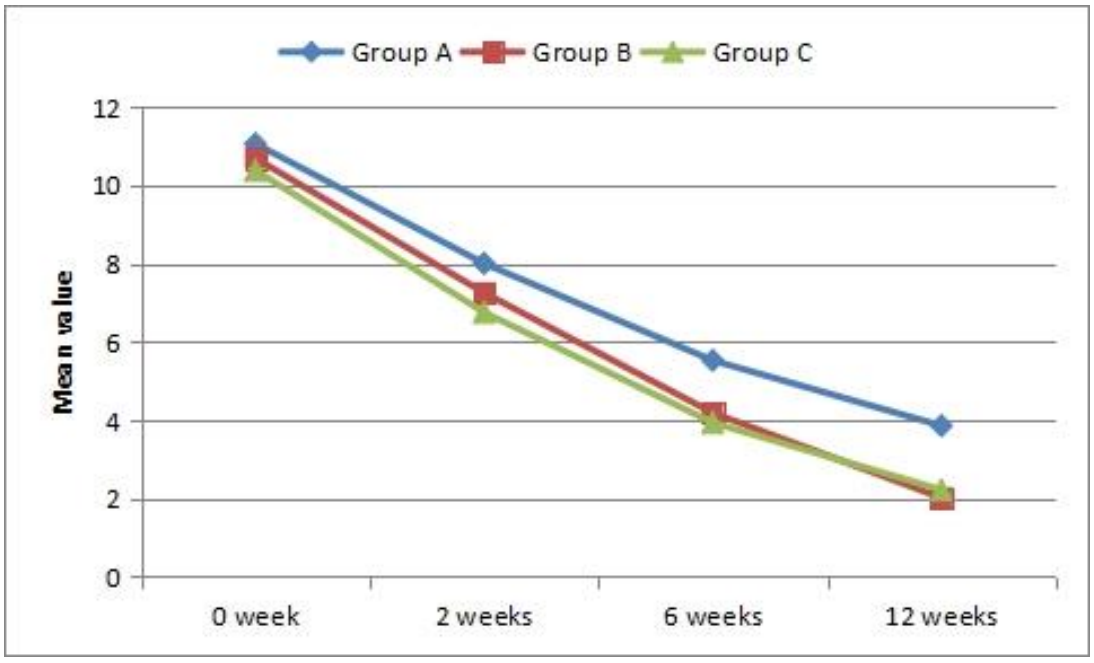

Fig. 3: Comparison of TSSS among the groups across the time periods

Table-4: Comparison of TOSS among the groups across the time periods

Groups	Group A (n=90)	Group B (n=90)	Group C (n=90)	p-value[1]	p-value[2]		
					Group A vs Group B	Group A vs Group C	Group B vs Group C
At entry	9.26±1.30	9.23±1.33	8.47±1.80	0.0001*	0.99	0.001*	0.002*
2 weeks	7.18±1.12	6.52±1.49	5.78±1.25	0.0001*	0.002*	0.0001*	0.0001*
6 weeks	4.99±0.90	3.46±0.73	3.53±0.88	0.0001*	0.0001*	0.0001*	0.81
12 weeks	3.10±0.49	1.18±0.38	2.00±0.21	0.0001*	0.0001*	0.0001*	0.0001*

[1]ANOVA test, [2]Post-hoc tests, *Significant

Table-4 & Fig.4 shows the comparison of TOSS among the groups across the time periods. The analysis of variance revealed that there was significant (p=0.0001) difference in TOSS among the groups at all the time periods. The post-hoc tests showed that TOSS was significantly (p<0.01) different between Group A & Group C and Group B and Group C at entry.

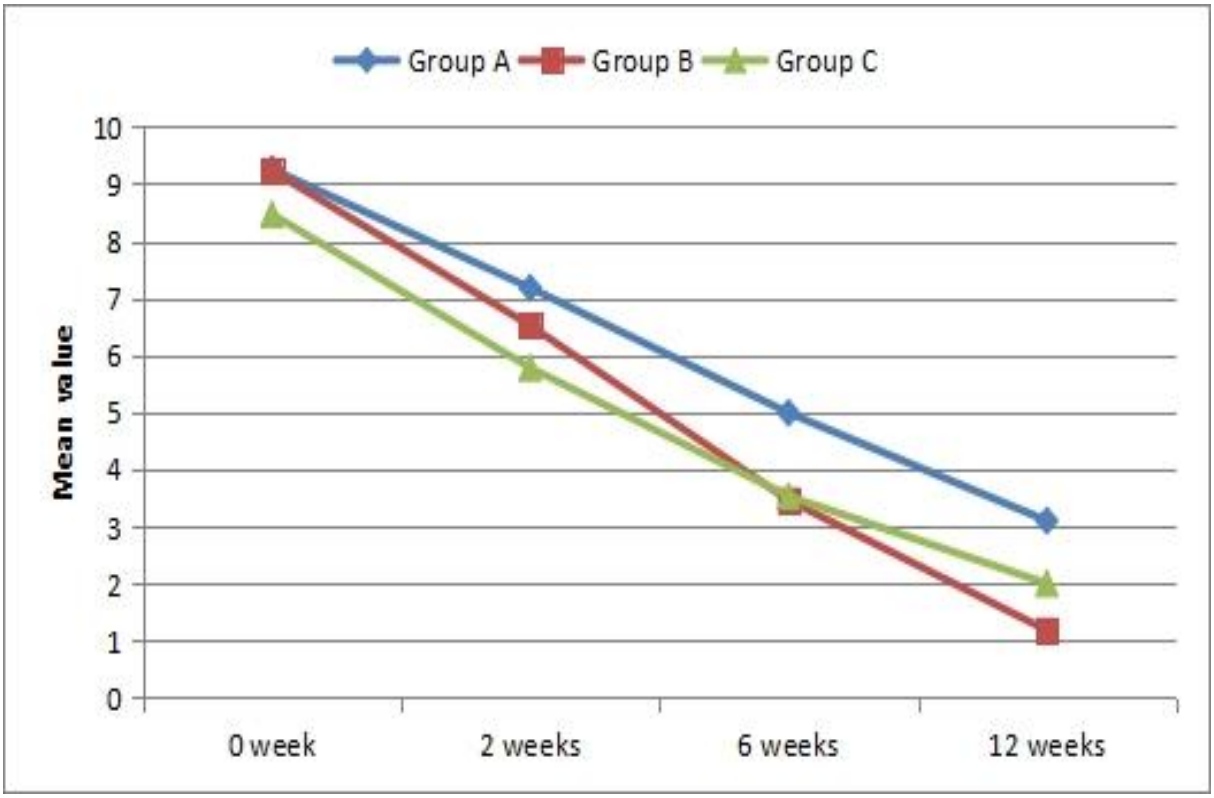

Fig. 4: Comparison of TOSS among the groups across the time periods

Table-5: Comparison of mean change in TSSS in groups from entry to subsequent time periods

Time period	Group A (n=90)		Group B (n=90)		Group C (n=90)	
	Mean change	p-value[1]	Mean change	p-value[1]	Mean change	p-value[1]
At entry to 2 weeks	3.05±1.19	0.0001*	3.44±1.18	0.0001*	3.63±0.99	0.0001*
At entry to 6 weeks	5.53±1.47	0.0001*	6.51±1.61	0.0001*	6.44±1.38	0.0001*
At entry to 12 weeks	7.21±1.03	0.0001*	8.67±1.25	0.0001*	8.16±1.28	0.0001*

[1]Paired t-test, *Significant

Table-5 & Fig.5 shows the comparison of mean change in TSSS in groups from entry to subsequent time periods. There was significant (p=0.0001) mean change in TSSS from 0 week to subsequent time periods in all the groups.

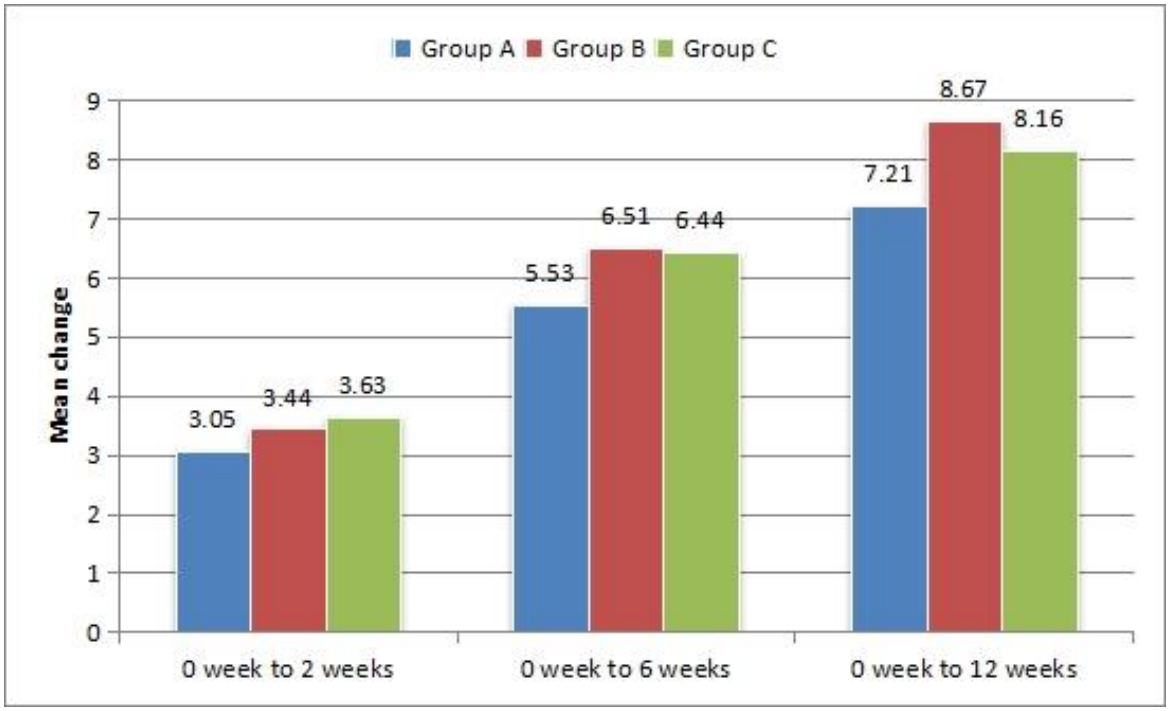

Fig. 5: Comparison of mean change in TSSS in groups from entry point to subsequent time periods

Table-6: Comparison of mean change in TOSS in groups from entry to subsequent time periods

Time period	Group A (n=90)		Group B (n=90)		Group C (n=90)	
	Mean change	p-value[1]	Mean change	p-value[1]	Mean change	p-value[1]
At entry to 2 weeks	2.07±0.92	0.0001*	2.71±1.49	0.0001*	2.68±1.28	0.0001*
At entry to 6 weeks	4.26±1.23	0.0001*	5.77±1.33	0.0001*	4.93±1.38	0.0001*
At entry to 12 weeks	6.15±1.31	0.0001*	8.05±1.29	0.0001*	6.46±1.81	0.0001*

[1]Paired t-test, *Significant

Table-6 & Fig.6 shows the comparison of mean change in TOSS in groups from entry point to subsequent time periods. There was significant (p=0.0001) mean change in TOSS from entry point to subsequent time periods in all the groups.

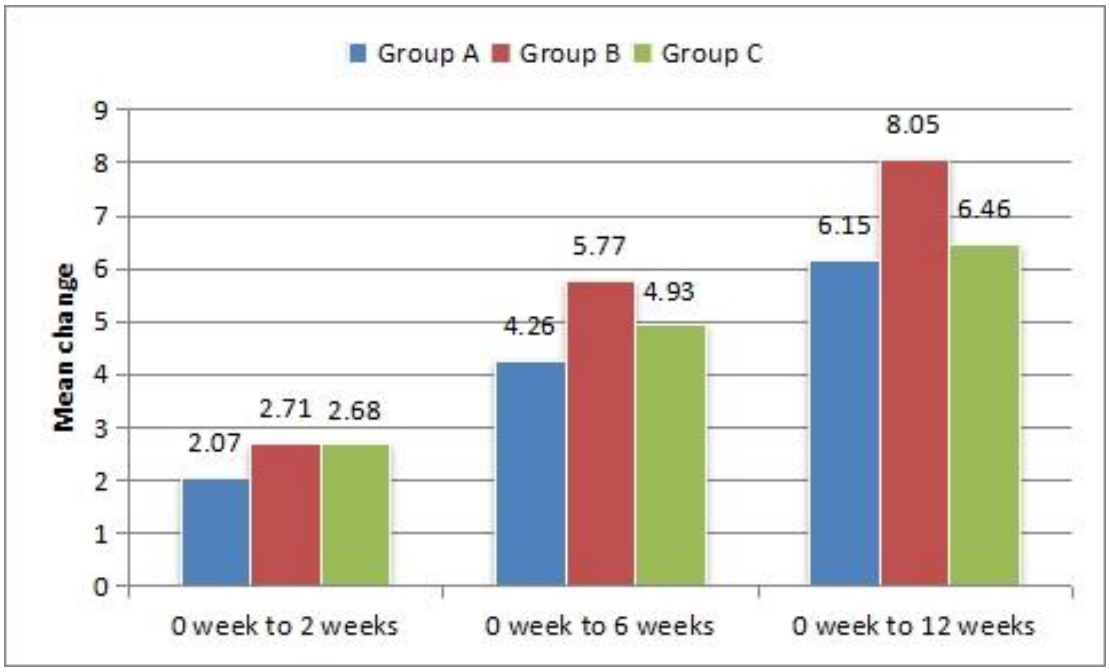

Fig. 6: Comparison of mean change in TOSS in groups from entry point to subsequent time periods

DISCUSSION

Vernal kerato-conjunctivitis (VKC) is a condition affecting young adults, particularly prevalent in tropical regions during the spring season, earning it the nickname "spring catarrh." In northern India, where VKC is a chronic burden, the morbidity and productivity of affected individuals are significantly impacted. While blindness is rare, managing VKC poses challenges for ophthalmologists, especially in cases resistant to conventional treatments.[6-9]

Various treatment modalities, including topical antihistamines, mast cell stabilizers, NSAIDs, corticosteroids, cyclosporine, Rebamipide, and tacrolimus, have been explored. However, long-term relief remains elusive, especially for severe or refractory cases. Surgical approaches like excision and cryodestruction of cobblestone papillae have been abandoned due to the risk of severe scarring.[10-13]

In a study focusing on different age groups, VKC patients aged 4 to 20 years were categorized based on the type of eye drops used. Significant age variations were observed, with Rebamipide, Cyclosporine, and Olopatadine groups having mean ages of 13.64, 11.84, and 8.69 years, respectively. The gender distribution showed a higher prevalence in males across all groups. In a study conducted by Çalişir et al. in 2016, it was found that the mean age of VKC patients was 11.83 ± 4.70 years (6–24 years).[14-15]

Symptom improvement was assessed using the BLEIK Grading score system. Rebamipide demonstrated marked improvement over 12 weeks, with a significant reduction in Bleik scores. Cyclosporine and Olopatadine also showed effectiveness, with Cyclosporine being more potent in the short term. Özcan et al. reported that CsA 0.05% significantly reduced symptom severity and clinical findings with a 6-month treatment. It also reduced the need for steroids. Thus, low-dose CsA has been recommended as an escape agent from steroids in VKC treatment.[16-19]

Objective signs, evaluated through the Total Objective Ocular Sign Score (TOSS), revealed improvements in conjunctival congestion, limbal papilla, Trantas spots, punctate keratitis, and limbal infiltration. Rebamipide exhibited consistent improvement over 12 weeks, and although Cyclosporine was more effective in the short term, long-term efficacy was similar between Cyclosporine and Olopatadine.This result is further supported by a study conducted by Trinh Khuu et al, showed a significant reduction in signs, symptoms, and tear levels of eosinophil cation protein in VKC patients after 2 weeks of using CsA four times daily.[20-21]

CONCLUSION

In conclusion, vernal kerato-conjunctivitis (VKC) is a debilitating condition necessitating a treatment ensuring long-term efficacy and safety. Our study demonstrated a statistically significant reduction in VKC clinical symptoms and signs scores across three treatment groups (Rebamipide, Cyclosporin, and Olopatadine). Topical administration, along with artificial tear and soft steroid, revealed equal effectiveness in symptom alleviation, with no serious adverse effects. Common side effects were mild and varied among groups. Rebamipide, Cyclosporine, and Olopatadine exhibited similar efficacy and safety profiles. Larger multicentric studies are essential for conclusive determination of individual drug regimen superiority in VKC patients.

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