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A COMPARISON OF EFFICACY OF MAST CELL STABILIZER (4% SODIUM CROMOGLYCATE) VERSUS TACROLIMUS OINTMENT PLUS MAST CELL STABILIZER (4% SODIUM CROMOGLYCATE)

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ABSTRACT

Vernal keratoconjunctivitis (VKC) is inflammation of the cornea seen usually in young children and adolescents, which often aggravates during summer and peaks in spring. Mast cell stabilizers are widely used long-term without any significant side effects. For patients who do not respond to mast cell stabilizers, the treatment has to be potentiated by another agent such as steroids like fluorometholone. Given the propensity of patients in Pakistan to self-medicate, the unsupervised and self-prescribed use of steroids is a real risk leading to hazards such as raised IOP, especially after long-term use. A safe long-term steroid alternative to supplement sodium cromoglycate thus assumes significant importance. This is why tacrolimus has been selected as a steroid-sparing agent in this study, The quantitative observational study was conducted in the Department of Paediatric Ophthalmology, Children's Hospital and Institute of Child Health, Children Hospital Lahore. The 4-week study included 60 male and female patients of primary VKC between 6 to 16 years of age. Using systemic random sampling the patients were divided into Group 1 (n=30), which was treated by using 4% sodium cromoglycate eye drops only, while in Group 2 (n=30), 0.03% tacrolimus eye ointment was also added. Pre- and post-treatment signs and symptoms of the patients were recorded and their difference was denoted as the Relief Score, The mean Relief Scores of Group 2 (n=30) were found to be significantly higher than those of Group 1 (n=30), with a p-value of less than 0.05. A combination of sodium cromoglycate with tacrolimus eye ointment was found to be more effective than sodium cromoglycate alone, Higher efficacy was observed in treating vernal keratoconjunctivitis when 0.03% tacrolimus eye ointment was added to 4% sodium cromoglycate eye drops. This makes tacrolimus a viable steroid-sparing agent, especially in prolonged or particularly resistant cases where steroid side effects are particularly troublesome.

Keywords: *Vernal Keratoconjunctivitis, Mast Cell Stabilizer, Sodium Cromoglycate, Immunosuppressive Agent, Anhydrous Tacrolimus.*

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is inflammation of the cornea which is usually bilateral, recurrent, and aggravates during summer and peaks in springtime.[1–3] It usually affects young children and adolescents. The affected individuals experience intense itching, lacrimation, and photophobia with ropy mucoid discharge. They also have giant cobblestone papillae on the superior tarsal conjunctiva and limbal conjunctiva as well This disease is usually self-limiting in nature and males are affected more with peaks at age 11 to 13. VKC can present in three forms; palpebral, limbal, and mixed. The palpebral form is characterized by cobblestone papillae affecting the superior tarsal conjunctiva, while the limbal form is characterized by gelatinous opacification of the superior limbus encroaching upon the cornea. The limbal form is characterized by Horner-Trantas dots in a circular pattern on the limbus.

There are currently a wide variety of options available to treat VKC but on the same note, these wide options also create some confusion as to which drug to use. Mast cell stabilizers are widely used on long-term basis without any significant side effects even for prolonged periods making it a favorite amongst ophthalmologists.[3] On the same hand there is a significant number of patients who don't respond to mast cell stabilizers and treatment has to be potentiated by another agent such as a steroid like fluorometholone. However, steroids have their side effects, most significant being raised IOP after long-term use.[4] Therefore, in a country such as Pakistan where patients self-medicate, it becomes necessary to give patients another safe option without the hazards of prolonged steroid use. It is for this reason that tacrolimus has been selected in this study as a steroid-sparing agent.[5] Tacrolimus, also known as fujimycin or FKS06, is an immunosuppressive drug used mainly after allogeneic organ transplant to lower the risk of organ rejection. Historically tacrolimus was used in Liver transplant cases as an immunosuppressive agent. It is mostly used in autoimmune skin disorders such as vitiligo and atopic dermatitis. As compared to steroids, it is equally effective without damaging the skin which usually happens with chronic topical steroid use. Numerous clinical trials have taken place to prove the efficacy of tacrolimus in eye disorders such as Mooren's ulcer, scleritis and cicatricial conjunctivitis as well as VKC.[5–12] Tacrolimus is available as eye ointment in concentration of 0.03% and 0.1%. No significant side effects have been documented except for slight burning sensation after application.

Subjects and Methods

The quantitative observational study was approved by the ethical review committee. It was carried out in Department of Paediatric ophthalmology, Children Hospital and Institute of Child Health, Children Hospital Lahore. The study lasted 4 weeks and included patients attending the outpatient department of paediatric ophthalmology.

The study included patients of both sexes, between 6 to 16 years of age and diagnosed with primary Vernal keratoconjunctivitis (VKC). Patients with history of dry eye disease, allergic conjunctivitis, ocular surgery within two months of study, corneal ulcer of infectious origin, active ocular herpes or having any abnormality of nasolacrimal system were excluded from the study.

Systematic random sampling was used to divide patients into 2 equal groups, with Group 1 (n=30) treated with 4 % sodium cromoglycate eyedrops, while Group 2 (n=30) treated with tacrolimus 0.03% ointment in combination with 4 % sodium cromoglycate eye drops.

The patients were interviewed for ocular symptoms such as itching, photophobia, watering and mucoid discharge. Slit lamp examination (SLE) was carried out to detect signs like conjunctival injection, limbitis and giant papillary conjunctivitis (GPC). These signs and symptoms were endorsed in the Data collection form. Follow up visits were carried out at the end of 1st, 2nd, 3rd and 4th weeks. Cases were assessed for overall treatment effect using a four-point grading system for signs and symptoms. Table 1 lists the grading scale used for quantifying severity of signs and symptoms.

Table 1: Grading of signs and symptoms

		0	1	2	3
Symptoms	Itching	Symptom free	Mild, occasional	Moderate, frequent	Severe, Constant
	Photophobia				
	Watering				
	Mucoid discharge				
Signs	Conjunctival injection	Nil	Mild	Moderate	Severe
	Limbitis				
	Giant papillary conjunctivitis (GPC)	Nil	(Not used)	Elevated papillae < 50% of upper palpebral conjunctiva	Elevated papillae > 50% of upper palpebral conjunctiva

SPSS version 27 was be used to analyse the data. Data was collected for Group 1 (Sodium cromoglycate), n=30 and Group 2 (Tacrolimus with Sodium Cromoglycate), n=30 (Table 2). There was no drop-out from the study.

Table 2: Summary

Group	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Group 1 (Sodium Cromoglycate)	30	100.0%	0	0.0%	30	100.0%
Group 2 (Sodium Cromoglycate with Tacrolimus)	30	100.0%	0	0.0%	30	100.0%

Relief scores for symptoms was calculated for both groups by subtracting sum of pre-treatment scores from sum of post-treatment scores. Mean Relief Score in Group 1 was 2.40 and 5.53 for Group 2 (Table 3).

Table 3: Descriptives

Group		Statistic	Std. Error
Group 1 (Sodium Cromoglycate)	Mean	2.40	.243
	Skewness	.514	.427
	Kurtosis	.281	.833
Group 2 (Sodium Cromoglycate with Tacrolimus)	Mean	5.53	.328
	Skewness	.153	.427
	Kurtosis	-.507	.833

Table 4: Distribution of Data

Group	Kolmogorov-Smirnova			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Group 1 (Sodium Cromoglycate)	.154	30	.067	.923	30	.032
Group 2 (Sodium Cromoglycate with Tacrolimus)	.183	30	.011	.957	30	.254

a. Lilliefors Significance Correction

Distribution of these scores was assessed and scores of Group 2 were not found to be normally distributed, with Kolmogorov-Smirnov p-value at less than 0.05 as shown in Tables 3 and 4. Therefore, Mann-Whitney U test was used to compare the distribution of Relief Scores in both groups. Null hypothesis (H_0) stated that distribution of Relief Scores is the same in both Groups. Alternate hypothesis (H_1) stated that Relief Scores in Group 2 would be better that in Group 1. A p-value of <0.05 was taken as statistically significant.

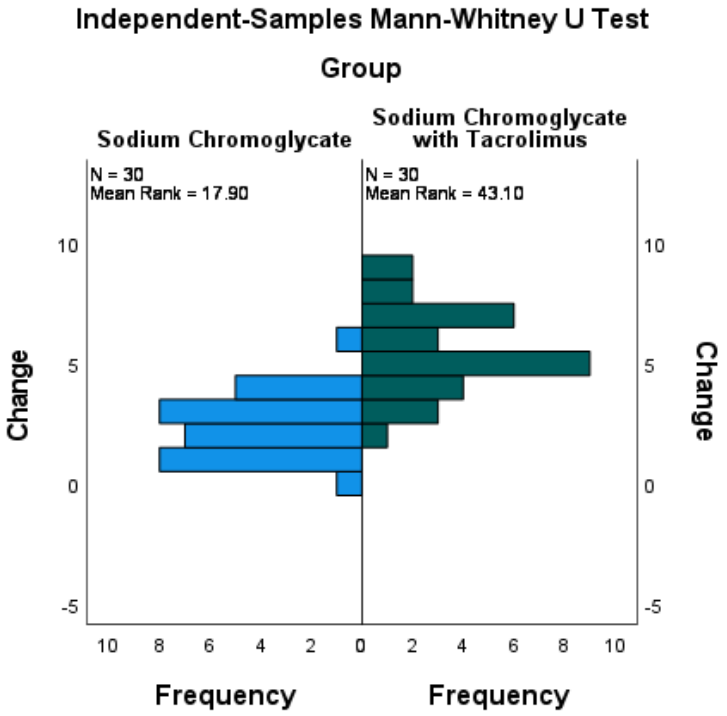
Results

The mean Relief Scores of Group 2 (n=30) were found to be significantly higher than those of Group 1 (n=30), with a p value of less than 0.05 (Table 5 and Figure 1). Null hypothesis was rejected and Alternate Hypothesis (H_1) was accepted.

Table 5: Hypothesis Testing

Null Hypothesis	Test	Sig.[a,b]	Decision
The distribution of Relief Scores is the same across categories of Group 1 & 2.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.

a. The significance level is .050.
b. Asymptotic significance is displayed.



Discussion

Patients who have been prescribed topical steroids in the past for VKC tend to self-medicate when the condition recurs. Because of the quick relief in symptoms, the patients often use steroids for prolonged periods of time. This renders then vulnerable to the risks of side effects. Data for topical steroid misuse in Pakistan is not available, but a study in India found out that out of 240 patients (ages between 10-17 years) using topical steroid preparations for VKC, 47 patients (40.4%) or 92 eyes, had steroid induced ocular hypertension. Another 37.2% had cataract, 6.3% keratoconus and shield ulcer in 2.1% eyes examined.[13]

In another study, 4.7% of children with paediatric glaucoma were diagnosed with steroid induced glaucoma (SIG). Of these, 87% had been

prescribed topical steroids for VKC. The median duration of steroid use was 18 months (with a range between 1 month to 8 years), with 52% using topical steroids for more than a year.[14]

Steroid sparing agents have been used for various ophthalmic conditions and two common ones include Cyclosporin and Tacrolimus. Topical cyclosporine A has been used as a steroid-sparing drug. However, in roughly 7-10% of cases, it has been ineffective. A study was carried out to evaluate the efficacy of 0.1% topical tacrolimus in patients with resistant VKC who did not respond adequately to 1% Cyclosporin A eyedrops. A significant improvement in signs and symptoms of VKC scores was observed with 0.1% Tacrolimus eye ointment, with p-value less than 0.001.[15]

In a double masked study comparing the use of cyclosporin A and Tacrolimus as monotherapy for VKC, it was found that improvement of Total subjective symptom scores (TSSS) in patients on Tacrolimus was 86.49% while for cyclosporine it was 79.04%. The difference between the two was judged to be not statistically significant. Similarly, Total objective ocular signs (TOSS) reduced for both drugs by almost the same degree.[16]

In a 4-week randomized, clinical trial of tacrolimus eye drops 0.1% in severe allergic conjunctivitis, The most frequent adverse event in the tacrolimus group was mild irritation in the eyes when the medicine was instilled. This was otherwise well-tolerated.[17]

Incidence or reactivation of Herpes Simplex infection has been postulated as a consequence of long-term use of Tacrolimus. However in a studying of corneal transplant patients, no incidents of herpes simplex virus infection or reactivation were seen, with the longest follow-up being 4 years.[18]

Conclusion

Higher efficacy was observed in treating vernal keratoconjunctivitis when 0.03% tacrolimus eye ointment was added to 4% sodium cromoglycate eye drops. This makes tacrolimus a viable steroid sparing agent, especially in prolonged or particularly resistant cases where steroid side effects would be particularly troublesome. The low incidence of side effects make it an even more attractive option, particularly in children.

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