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Comparative Study between Olopatadine 0.1% and Cyclosporine 0.05% Eye Drops in Children with Vernal Keratoconjunctivitis.

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ABSTRACT

Ocular allergy is a frequently encountered pathology in ophthalmological practice, with an increase in number of patients noticed in the recent years. VKC is in response to non-specific allergens and is mediated mainly by Th2 cells, but mast cells and eosinophils also play a major role. Various causes have been considered for the disease such as genetics, air pollution, pollens and pets.Avoidance of allergens and hygiene plays a key role in the management of VKC.The main aim of this study is to compare the efficacy of cyclosporine (0.05%) and olopatadine (0.1%) in VKC in children in a tertiary health care centre. Around 20 patients (40 eyes) with VKC who visited Ophthalmology Out-Patient department of a tertiary care hospital from May 2019 to August 2019. They were divided into 2 groups and advised for instillation of drops twice daily for 4 weeks and patients were assessed on 7th, 14th, & 28th day. Although there was significant reduction in subjective symptom ($p<0.05$) and objective sign score ($p<0.01$) at 2 weeks and 1 month of follow up when compared with baseline values. There was no difference in subjective symptom and objective signs score between the two groups at any of the follow up visits.In the course of the treatment in patients with VKC, both cyclosporine 0.05%and olopatadine 0.1%were found to be equally effective in alleviating signs and symptoms of VKC.

KEY WORDS: VKC, comparison olopatadine, cyclosporine, children

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a common severe, chronic recurrent sight threatening allergic eye disease, occurring mainly in children, mostly in the first decade of life. Thepresenting symptoms are characterized by itching, irritation, tearing, photophobia, hyperaemia, chemosis, and sticky

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mucous discharge. An important clinical sign of VKC is the presence of giant papillae showing cobblestones appearance on the upper tarsal conjunctiva. The signs and symptoms show exacerbations during the spring season. White dots consisting of eosinophils and epithelial debris, known as Horner- Trantas dots, is characteristic of limbal form.Some patients with VKC have spontaneous resolution of their symptoms. However, others may require treatment to control the course of the disease. Untreated VKC can lead to irreversible corneal changes that profoundly impair vision. Recurrences for several years with development of severe dry eye and corneal shield ulcer with scarring can occur.Previous studies suggest the pathophysiological mechanism of allergic inflammation probably playing a major role in the aetiology of VKC. However, VKC pathogenic mechanism is more complex than a classic type 1 immunoglobulin-E (IgE)-mediated allergic disease.VKC is an allergic inflammatory disease involving mast cells, eosinophils, lymphocytes, dendritic cells, basophils and macrophages that infiltrate the conjunctival epithelium and corneal stroma [1,2]. Pharmacological treatment options for VKC include antihistamines, mast-cell stabilizers, dual-acting agents,corticosteroids and immunomodulators such as Cyclosporine A and Tacrolimus.Topical corticosteroids are reported to be very effective in the treatment of VKC. However, they may lead to steroid-induced glaucoma and cataracts in patients with prolonged use restricting their use for selected patients. Therefore, these drugs should not be administered as a first-line treatment in VKC patients. [3,4,5] The aim of this study is to comparethe effects of olopatadine 0.1% and cyclosporine 0.05% on the signs and symptoms.Olopatadine (0.1%) acts as a selective antagonist of the H1 receptor, thus stabilising mast cells and histamine release.Cyclosporine (0.05%) eye drops is an immunomodulator which blocks the T cell proliferation and Interleukin 2 production, thereby preventing steroid induced complications in VKC patients. There are no serious side effects of these drugs except for mild burning and stinging sensation after initial application.Injudicious use of steroids leads to vision threatening complications like ocular hypertension and glaucoma in children of VKC.

METHODOLOGY

A randomised prospective study conducted on 20 patients (40 eyes) of VKC who visited OphthalmologyOut-Patient department of a tertiary care hospital from May 2019 to August 2019.Based on the previous hospital records, the approximate number of potential Eligible subjects in the study age group attending the study setting during the datacollection period were considered as 200. Hence a finite population correction was applied for 200. Other parameters considered for sample size calculation were 99% and 95% confidence level.

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The required sample size to our study as per the calculation was 18. To account for a non-participation rate/ loss to followup rate of about 5%, another 2, subjects will be added to the sample size. Hence the final required sample size would be 20.

Inclusion criteria:Participants diagnosed with bilateral symmetrical VKC,age from 5-18 years

Exclusion criteria:Participants or their parents not willing to participate in the study, uncooperative patients,Contact lens wearers.

An informed consent form was obtained from the guardians of the patients prior to inclusion in the study. The study was approved by Institutional Ethical Committee. During enrolment, age, gender, and family history of an allergic disease of the participants were noted. A detailed history was taken about the onset of symptoms, duration, progression, recurrences and treatment taken. Allthe patients who participated in the study underwent a complete ophthalmological examination such as Uncorrected Visual Acuity (UCVA), Best Corrected Visual Acuity (BCVA), cycloplegicrefraction and a detailed slit lamp examination. Symptoms like itching, tearing, foreign body sensation and discharge were graded on a scale of 0 to 3 on the basis of grading system adopted by (Bleik et al)[6] as shown in Table 1. Patients were divided into Group Aconsisting of 20 eyes (Olopatadine 0.1%)and GroupB consisting of 20 eyes (Cyclosporine0.05%) and were advised toadminister drops twice daily for 4 weeks. Patients were assessedon 7, 14 and 28 day. Pre and post treatment average symptoms score was noted on each follow up by using a grading scale (Grade0-3) based on subjective assessment of severity of symptomsandobjective assessment of signs. Score was given to each patient fortheir grades of symptom / sign and by adding up, the total score ofeach patient was calculated. Descriptive analysis of data was carried out by mean for quantitative variables. The association between categorical explanatory variables and their outcome was assessed by comparing the mean values and unpaired t-test was applied to assess statistical significance. Statistical analysis was done using SPSS Software Version 22.

Table 1-Grading of symptoms and signs [6]

Grading of symptoms	
0	No symptoms
1+	mild symptoms of discomfort which were just noticeable
2+	moderate discomfort noticed most of the day but did not interfere with daily routine activities
3+	severe symptoms interfering with daily routine activities
Grading of Signs Conjunctival hyperemia	

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0	no evidence of bulbar hyperemia
1+	mild bulbar hyperemia
2+	moderate bulbar hyperemia.
3+	severe bulbar hyperemia
Palpebral conjunctival papillae	
0	no papillary hypertrophy of the palpebral conjunctiva
1+	mild papillary hypertrophy
2+	moderate papillary hypertrophy (hazy view of the deep tarsal vessels).
3+	severe papillary hypertrophy (deep tarsal vessels not visible in more than 50% of the surface).
Punctate keratitis	
0	no evidence of punctate keratitis
1+	one quadrant of punctate keratitis
2+	two quadrants of punctate keratitis
3+	three or more quadrants of punctate keratitis
Trantas'dots	
0	no evidence of dots.
1+	1 to 2 dots
2+	3 to 4 dots
3+	more than 4 dots
Limbal infiltration	
0	no evidence of limbal infiltrates
1+	less than 900 of limbal infiltrates
2+	less than 1800 of limbal infiltrate but more than 900.
3+	more than 1800 of limbal infiltrate.

RESULTS

Mean age of these children was 10.5years; the maximum age of the patients in our study was 15 years. Males (55%) were more in number than females (45%) as depicted in Table 2.Palpebral VKC was the most common form of presentation (55%),followed by limbal type VKC(25%) and mixed type (20%).Baseline total subjective symptom score in the Group A was 7.76(+/-2.67) and in Group B was 7.03(+/-2.70). Baseline total ocular sign score in both the groups were 4.67(+/-1.6) and4.72(+/-1.7) respectively as shown in Table 2. Themean signs and symptoms scores of both olopatadine-treated eyes and cyclosporine-treated eyes are as shown in Table 3 and Table 4.

Table2:Observed Parameters

S. No	Parameters	No of patients (%)		Total
		Group A (Olopatadine 0.1%)	**Group B (Cyclosporine0.05%)**	

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1	No of patients	N= 20 eyes	N=20 eyes	40 eyes
2	Sex -Male Female	12(60%) 8 (40%)	10 (50%) 10 (50%)	22 (55%) 18 (45%)
3	Age group 5-10 11-15	 6 (30%) 14 (70%)	 8 (40%) 12 (60%)	 14 (70%) 26 (65%)
4	Type of VKC Palpebral Limbal Mixed	 12 (60%) 5 (25%) 3 (15%)	 10 (50%) 5 (25%) 5 (25%)	 22 (55%) 10 (25%) 8 (20%)
5	Total subjective symptom score	7.76(+/-2.67)	7.03(+/-2.70)	
6	Total ocular sign score	4.67(+/-1.6)	4.72(+/-1.7)	

Table 3: Total Subjective Symptom Score

Follow up	**Group A (Olopatadine 0.1%)**	**Group B (Cyclosporine0.05%)**	**P value**
Day 0	7.16(5.31-8.35)	7.80(6.33-8.76)	p =0.42
Day 7	4.72 (3.69-5.04)	3.93(3.33-4.43)	p=0.11
Day 14	2.69(2.40-3.13) p=0.004	2.45(2.10-3.13) p=0.004	 p=0.53
Day 28	1.33(0.99-1.59) p=0.001	1.18(0.89-1.45) p=0.001	p=0.58

Table 4: Total Objective Sign Score

Follow up	Group A (Olopatadine 0.1%)	Group B (Cyclosporin 0.05%)	P value
Day 0	4.67(4.03-5.12)	4.72(3.99-5.05)	p=0.43
Day 7	4.20(3.63-4.72)	4.2(3.43-4.45)	p=0.55
Day 14	3.23(2.71-3.99) p=0.13	3.04(2.45-3.49) p=0.14	p=0.45
Day 28	2.74(2.34-3.32) p=0.03	2.53(1.92-3.02) p=0.03	p=0.27

The total subjective symptom score was comparedbetween both the groups. On Day 0 the subjective score was 7.16 and 7.80 for Group A and Group B respectively. On Day 7 the subjective score decreased and was 4.72 and 3.93 for Group A and Group B respectively. On day 14 the subjective score decreased further and was 2.69(p value 0.004) and 2.45 (p value 0.004) for Group A and Group B respectively. On day 28 of follow-up the subjective score decreased significantly and was 1.33(p value 0.001) and 1.18 (p value 0.001) for Group A and Group B respectively. Based on

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Received 05 March 2021; Accepted 01 April 2021.

total subjective symptom score, there was reduction in mean score from Day 7 onwards which was statistically significant at 2 weeks and 1 month of follow up ($p<0.05$) when compared with baseline values. But there was no statistically significant difference between the two groups at any of the follow up visits.

The total objective symptom score was compared between the Group A and Group B and we found the following results. On Day 0 the objective score was 4.67 and 4.72 for Group A and Group B respectively. On Day 7 the objective score was almost the same as Day 0 with minimal reduction in scores, 4.20 and 4.2 for Group A and Group B respectively. On day 14 the objective score decreased and was 3.23 (p value 0.13) and 3.04 (p value 0.14) for Group A and Group B respectively. On day 28 of follow-up the objective score decreased significantly and was 2.74 (p value 0.03) and 2.53 (p value 0.03) for Group A and Group B respectively. Based on total objective sign score there was decrease in the mean score in subsequent visits in both the groups and it was statistically significant when compared to baseline at 1 month of follow up($p<0.01$). There was no difference in objective signs score between the two groups at any of the follow up visits.

DISCUSSION

VKC is a severe chronic allergic inflammatory disease characterized by recurrent, bilateral, occasionally asymmetrical, seasonally exacerbating ocular inflammation. It may also be seen in severe chronic forms that can inflict irreversible corneal changes, profoundly impairing vision [7,5]. VKC decreases an individual's quality of life due to its disturbing long-term symptoms, to minimize it the management of allergic eye disease is aimed at blocking the release of allergic mediators in order to control the allergic inflammatory cascade and to prevent ocular surface damage secondary to the allergic response.Therefore, effective long-term treatment is necessary. The therapy administered to the patients should not only treat the disease but it should also be safe and protect the other ocular structures. Various modalities of treatment are available, the aim of which is to block the release of allergic mediators and control the allergic inflammatory cascade. Patients and parents should be instructed regarding the nature and duration of the disease, clinical characteristics and possible complications. Psychological support may be necessary in severe cases. The first line of VKC management, when possible, is the identification of allergens and avoidance of those environmental factors that may exacerbate the disease.Patients with VKC often have hypersensitivity to pollens and house dust, this can be prevented by avoiding growing plants indoors and keeping the environment at home clean. Avoiding exposure to nonspecific triggering factors, such as sun, wind, and salt water, with the use of sunglasses, hats with visors, and swimming goggles should be recommended. Frequent hand, face, and ear washing should also be suggested. Cold compresses may help as natural

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decongestant. Tear substitutes aid in stabilization of the tear film, act as an eyewash, and dilute the concentration of the allergens and mediators in tears [15].Prior to the advent of immunomodulators, the treatment of severe allergic conjunctivitis were antihistamines and/or steroids. Unfortunately, antihistamines alone are insufficient without concomitant steroid use. However, topical steroids put the patients at high risk of developing cataracts and glaucoma. Long term steroids usage is being replaced by immunomodulators.

In this study we compared the efficacy of olopatadine (0.1%) and cyclosporine (0.05%). Out of 20 patients (40 eyes) Males (55%) were more in number than females (45%). In comparison with the study by Mita saha et al out of 134 patients 88(65.63%) were males and 46(34.33%) werefemales [37].The mean age of these children was 10.5years; the maximum age of the patients in our study was 15 years. 11- 15 years 94 (70.15%) was also the maximum age group with VKC reported by mita saha in their study [37].A significant improvement in symptoms was noted at 2 weeks and 1 month of follow up in eyes treated with cyclosporine as well as those treated with olopatadine, when compared to baseline values ($p<0.05$). The results were not statistically significant in the eyes treated with cyclosporinewhen compared to eyes treated with olopatadine. Based on subjective signs, significant improvement in signs was noted at 1 month of follow up in eyes treated with cyclosporine as well as those treated with olopatadine, when compared to baseline values but the results were not statistically significant between the two groups.When the antihistaminic medications were compared, it was reported that Olopatadine hydrochloride 0.1% caused less discomfort for patients during the use of the drug. (8). As inour study there was no ocular side effects between the two groups. This study compared the efficacy of topical cyclosporine in the treatment as well as a measure for the preventive prophylaxis. Mita saha et al reported in their study that Cyclosporine had 46.88% and 65.63% of patients relieved from symptoms in 1 and 2 weeks respectively as compared to olopatadine, having 60% in 1 week and 65% in 2 weeks with a study population of 134. On 4 weeks follow-up, Cyclosporine showed significant improvement in symptoms score with 78% patients relieved as compared to 68% patients of olopatadine [37]. There are several studies showing the efficacy of both Olopatadine and Cyclosporine, in the treatment of VKC. Eiichi Uchio et al reported that following 2 months treatment with olopatadine hydrochloride 0.1% there is relief in the signs and symptoms of VKC. Also, it reduces the number of goblet cells, which, in turn, decreases the amount of mucus discharge in VKC during treatment [34].It is reported that Olopatadine is inadequate to control the symptoms in severe cases and to prevent recurrence. Development of tolerance to Cyclosporine and high cost is a disadvantage of the drug [5].Itwas shown that Cyclosporine inhibited inflammatory cell infiltration and fibrosis by suppressing T helper cells (Th2)

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cytokine release in allergic conjunctivitis. It is known that Cyclosporine A has an immunomodulator effect and is effective in the improvement of symptoms in the treatment of VKC [6,9-11]. Ben Eli et al suggested that high concentration olopatadine 0.77% had longer duration of action, better efficacy on ocular itch, and a similar safety profile to low-concentration olopatadine 0.2%. The new formulas of topical dual-action agents present longer duration of action, leading to a decreased frequency of use [35]. Knatova et al in his study assessed regarding the subjective symptoms such as itching, tearing, Foreign body sensation and mucous discharge, no statistically significant differences were found between the baseline and the 3rd, 6th, 12th, and 18th months when comparing the Olopatadine and Cyclosporine A groups. While no difference was seen regarding the Foreign Body sensation according to the month in the Olopatadine group, a significant decrease was observed with the treatment in the Cyclosporine A group. A significant decrease was observed regarding the itching, tearing, and mucous discharge in both of the groups with the treatment [36].

Pucci et al in his study for a period of 7 years, investigated the long-term safety and efficacy of Cyclosporine A 1% and 2%. In their study, it was reported that Cyclosporine A was effective in the improvement of the children's symptoms on average over 24 months and no side effects were seen due to the treatment.Cyclosporine eye drops, either at 1% or 2% concentrations, resulted safe and effective for long-term treatment of VKC in 156 children. [12]. In a prospective study comparing topical Cyclosporine A 2% and Dexamethasone 0.1%, including 366 VKC cases, no significant difference was seen in the decrease of symptoms over 4 weeks [5].While corticosteroids are known to be effective in controlling the signs and symptoms and resolving inflammation, they are associated with serious complications, including increased intraocular pressure (IOP) requiring glaucoma management. Saurbhi Khurana et al, in his study reported that Olopatadine was effective in treating papillary conjunctivitis related to contact lens wear. Olopatadine is effective in alleviating signs and symptoms of contact lens-induced mild to moderate papillary conjunctivitis and is comparable with fluorometholone in efficacy [13]. It has also been shown that Cyclosporine A is effective in causing regression of the objective symptoms, particularly the giant papillae on the tarsal conjunctiva due to VKC. The inhibitory effect of Cyclosporine A in the development of conjunctival fibrosis and the development of corneal vascularization [14]. Further studies are required to establish the efficacy of both the drugs in terms of recurrence in the patients.

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Figure 1: PALPEBRAL FORM - VKC

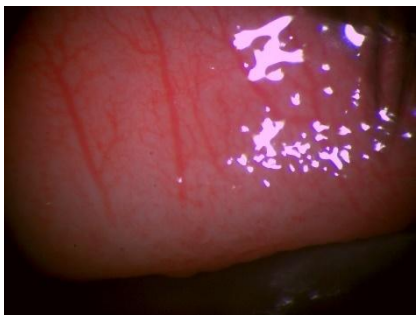
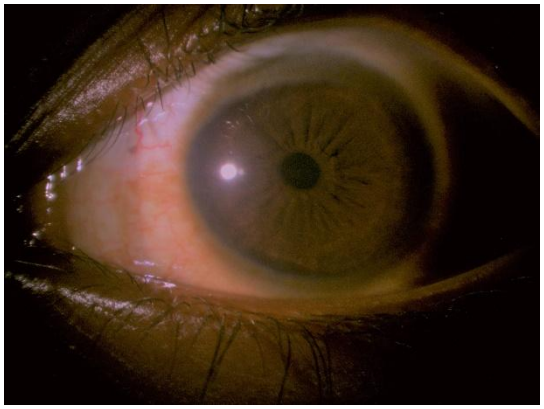


Figure 2:PSEUDOGERONTOXON- VKC



CONCLUSION

In the course of the treatment in patients with VKC, both cyclosporine 0.05%and olopatadine 0.1%were found to be equally effective in alleviating signs and symptoms of VKC.Thus, the use of Olopatadine (0.1%) and Cyclosporine (0.05%) has better visual outcome and less complications in comparison with steroids induced complications in treatment of VKC.

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