Original Article

A Randomized Controlled Trail on the Efficacy of Topical Olopatadine Hydrochloride 0.1% and Ketotifen Fumarate 0.025% for the Relief of Symptoms of Vernal Keratoconjunctivitis

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ABSTRACT

Objective: This study was aimed at comparing efficacy of topical Olopatadine Hydrochloride 0.1% and Ketotifen Fumarate 0.025% for the symptomatic relief of VKC related symptoms at Bahawal Victoria Hospital, Bahawalpur.
Study Design: Randomized controlled trial study.
Place and Duration of Study: This study was conducted at the out-patient department (OPD) of ophthalmology, Bahawal Victoria Hospital, Bahawalpur from October 2019 to March 2020.
Materials and Methods: A total of 186 patients of both gender with VKC were enrolled. Through computer generated numbers, patients were randomly divided into 2 equal groups (93 cases in each group). In Group A, topical olopatadine HCL 0.1% was advised 6 hourly whereas patients of Group-B were advised topical ketotifen fumarate 0.025% 6 hourly. All patients were advised a follow up on 7th and 28th day while final outcome was noted on 28th days following the start of treatment. Efficacy among both treatment groups were noted in the form of relief from VKC related symptoms (itching, watering, foreign body sensation, photophobia).
Results: Out of a total of 186 patients, there were 111 (59.7%) boys 75 (40.3%) girls. Overall, mean age was 9.47±3.46 years (ranging from 5 to 19 years). Majority of the patients, 104 (55.9%) were below or equal to 10 years of age. At the end of the study period, significantly more number of patients in Group-A had relief in itching, watering and foreign body sensation in comparison to patients in Group B ($p<0,05$). Overall compliance with treatment in both study groups was excellent and no adverse effects were reported in both study groups
Conclusion: Compared to ketotifen fumarate 0.025%, efficacy of olopatadine HCL 0.1% was better in the form of relief of VKC related symptoms. Apparently, no side effects were reported among both study groups while overall compliance with both study drugs was excellent.
Key Words: Vernal keratoconjunctivitis, efficacy, olopatadine hydrochloride 0.1%, ketotifen fumarate 0.025%.

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INTRODUCTION

Vernal keratoconjunctivitis (VKC) was 1st described about 150 years ago and it is known to be a chronic inflammatory disease related to ocular surface.[1]

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VKC is one of the commonest and worst types of allergic conjunctival diseases. Due to the chronic nature of VKC, it is described to damage cornea that may result in sight-threatening complications.[2]

If not treated timely, because of its chronic nature, it can damage the cornea, resulting in sight-threatening complications[3] These kinds of allergies induce type-1 hypersensitivity reactions due to mediation by IgE and most commonly in response to different kinds of environmental allergens.[4]

In developed countries, prevalence of VKC is 0.1% to 0.5% while exact prevalence of VKC in South Asian Countries is not known.[5]VKC is most commonly observed among 5 to 15 years age groups and is usually bilateral and recurrent allergic conjunctivitis. VKC predominantly affect boys and not common beyond the age of 25 years.[6]

Genetic predisposition as well as history of atopy and non-specific hypersensitivity is commonly linked with VKC.[7] VKC is more commonly found to occur in hot

weather while occurrence during winter is not frequent. Clinical types of VKC include palpebral, limbal and mixed types. Most commonly noted symptoms of VKC are intense itching, lacrimation, redness, foreign body sensation, photophobia and thick mucoid discharge.[8]

Most commonly endorsed treatment options for the treatment of VKC include topical steroids, anti-histamines as well as mast cell stabilizers. Ketotifen fumarate ophthalmic solution is a benzocycloheptathiophene derivative utilized for relieving symptoms of VKC. Ketotifen fumarate inhibits hitamin H1 receptors, induces mast cell stabilization and prevent eosinophil buildup. Olopatadine hydrochloride 0.1% is a dibenzoxepin derivate that acts via a selective antagonistic reaction on the H1 histamine receptor atthe end organ and stabilize conjunctival mast cells to result in inhibition of the release of pro-inflammatory mediators.[9]

In 2013, a study comparing olopatadine 0.1% with ketotifen fumarate 0.025% noted relief of itching and redness as 100% vs. 83.3% and 96.7% vs. 85.0% respectively in both the study groups.[10]Topical Olopatadine Hydrochloride 0.1% and Ketotifen Fumarate 0.025% are freely available and affordable therapeutic options for the treatment of VKC but in the past 5 years, no study comparing Topical Olopatadine Hydrochloride 0.1% and Ketotifen Fumarate 0.025% has been done in Pakistan to note the symptomatic relief provided by these drugs in patients with VKC. This study was aimed at comparing efficacy of topical Olopatadine Hydrochloride 0.1% and Ketotifen Fumarate 0.025% for the symptomatic relief of VKC at Bahawal Victoria Hospital, Bahawalpur. The results of this study will help us deciding better options aiming symptomatic relief of VKC related symptoms.

MATERIALS AND METHODS

Approval from Institutional Ethical Review Committee was taken for this randomized controlled trial. The study was conducted between 1st October 2019 to 31st March 2020 at out-patient department (OPD) of ophthalmology, Bahawal Victoria Hospital, Bahawalpur.

A sample size of 186 cases (93 cases in each group) considering 2-sided significance level as 95%, power 80% and efficacy of olopatadine HCL 0.1% as 96.7% and ketotifen fumarate 0.025% as 85.0% for the relief of redness.[10]

During the study period, a total of 186 patients with VKC were enrolled. VKC was labeled as presence of conjunctival papillae of >1 mm diameter over the upper tarsal plate along with limbal papillae with or without Trantas dots.[2] Patients coming with seasonal allergic conjunctivitis and perennial allergic conjunctivitis were excluded. Patients missing follow up or not completing the treatment as per advice were also excluded from this study. Written consent was taken from all the study participants or parents/guardians. Through computer generated numbers, patients were randomly divided into 2 equal groups (93 cases in each group). In Group A, topical olopatadine HCL 0.1% was advised 6 hourly whereas patients of Group-B were advised topical ketotifen fumarate 0.025% 6 hourly. All patients were advised a follow up on 7th and 28th day while final outcome was noted on 28th days following the start of treatment. Efficacy among both treatment groups were noted in the form of relief from VKC related symptoms (itching, watering, foreign body sensation, photophobia).

Data analysis was done using computer software SPSS version 26.0. Age was represented in terms of mean and standard deviation and comparison in between study groups was made employing independent sample t-test. Qualitative variables like gender and relief in symptoms were highlighted as frequencies and percentages while chi square test was applied to compare these. P value less than or equal to 0.05 was considered as significant.

RESULTS

Out of a total of 186 patients, there were 111 (59.7%) boys 75 (40.3%) girls showing a male to female ratio of 1.3:1. Overall, mean age was 9.47±3.46 years (ranging from 5 to 19 years). Majority of the patients, 104 (55.9%) were below or equal to 10 years of age. In terms of disease pattern of VKC, most of the patients, 99 (53.2%) were palpebral, 50 (26.9%) bulbar and remaining 47 (25.3%) mixed. Table No.1 showing that there was no significant difference between characteristics of patients in the both study groups (p>0.05).

Table No.1: Characteristics of Patients with VKC among both study groups (n=186)

Characteristics		Group-A (n=93)	Group-B (n=93)	P-Value
Gender	Boys	58 (62.4%)	53(57.0%)	0.4548
	Girls	35 (37.6%)	40 (43.0%)	
Age Groups (years)	≤10	56 (60.2%)	48 (51.6%)	0.2374
	>10	37 (39.8%)	45 (48.4%)	
Disease Pattern	Pal-pebral	48(51.6%)	51 (54.8%)	0.5903
	Bulbar	28 (30.1%)	22 (23.7%)	
	Mixed	17 (18.3%)	20 (21.5%)	

Table number 2 is showing the comparison of relief of symptoms among patients of VKS in both study groups at the end of study period after 28 days of treatment. Significantly more number of patients in Group-A had relief in itching in comparison to patients in Group B (98.9% vs. 903%, p=0.0093). In terms of watering, significantly more number of patients in Group-A reported relief when compared to patients in Group-B (98.9% vs. 87.1%, p=0.0016). Foreign body sensation was significantly more relived among study participants

in Group-A when compared to Group-B (96.8% vs. 88.2%, p=0.0262). In terms of redness and photophobia, no significant difference in terms of relief among study groups was noted (p>0.05). Overall compliance with treatment in both study groups was excellent and no adverse effects were reported in both study groups.

Table No.2: Comparison of Relief of Symptoms among Patients of VKS in both study groups at the end of study period (n=186)

Symptoms	Relief	Group-A (n=93)	Group-B (n=93)	P-Value
Itching	Yes	92 (98.9%)	84 (90.3%)	0.0093
	No	1 (1.1%)	9 (9.7%)	
Redness	Yes	91 (97.8%)	86 (92.5%)	0.0875
	No	2 (2.2%)	7 (7.5%)	
Watering	Yes	92 (98.9%)	81 (87.1%)	0.0016
	No	1 (1.1%)	12 (12.9%)	
Foreign Body Sensation	Yes	90 (96.8%)	82 (88.2%)	0.0262
	No	3 (3.2%)	11 (11.8%)	
Photophobia	Yes	59 (63.4%)	56 (60.2%)	0.6507
	No	34 (36.6%)	37 (39.8%)	

DISCUSSION

VKC is known to be a frequent and common disorder in South Asian Region. Treatment of VKC has evolved in the last few decades whereas conventional treatment options like antihistamines, mast-cell suppressors as well as steroids are still considered valuable. Clinicians handling VKC around the world have always been interested in addressing exacerbations, reduction of symptoms and avoidance of drugs related complications. In recent decades, improved understanding of the pathogenesis of VKC and researches conducted around the world has led to better management of VKC.[11]

Among patients of VKC, mast cells are thought to play an important role to cause signs and symptoms as raised levels of histamine, tryptase, Prostaglandin D2 and leukotriene C4 in the tears of cases having VKC following conjunctival allergen exposure.[12]Drugs having numerous mechanisms of action are now accessible like olopatadine HCL and ketotifen fumarate. As both these drugs are in our use to treat VKC and researchers from around the world have indicated acceptable efficacy of these therapeutic options in multiple findings.[6,9] Yet, dilemma exists that which option is better than the other as not much local work has been done in this regard.

In the present study, both study drugs provided good overall relief of symptoms but olopatadine HCL proved significantly superior in terms of relieving VKC related symptoms when compared with ketotifen fumarate. A local study comparing olopatadine HCL 0.1% with ketotifen fumarate 0.025% found significantly better efficacy of tolerability among patients using olopatadine HCL 0.01%.[13] Ahmad I et al from Peshawar also found similar results where they noted patients using olopatadine HCL to have better relief of symptoms when compared to ketotifen fumarate.[10]Ketaralis CH also noted olopatadine HCL 0.1% to impart better efficacy in comparison to ketotifen fumarate among allergic conjunctivitis cases.[14] Auguilar AJ in his study also noted olopatadine HCL 0.1% to have better efficacy and tolerability against seasonal allergic conjunctivitis when compared to ketotifen fumarate 0.05%.[15]Olopatadine HCL is known for its dual mode of action in terms of H1-antihistamine/mast cell stabilization effects.[16,17] In other trials, olopatadine has also been found superior when compared to sodium cromoglycate for the treatment of VKC.[16] Leonardi A and Zafirakis P in their double-masked trial reported olopatadine HCL 0.1% to have better efficacy when compared with ketotifen fumarate.[18]

More studies involving multiple study centers and different sets of treatment with prospective interventional design will further add to the findings of this study.

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CONCLUSION

Compared to ketotifen fumarate 0.025%, efficacy of olopatadine HCL 0.1% was better in the form of relief of VKC related symptoms. Apparently, no side effects were reported among both study groups while overall compliance with both study drugs was excellent.

Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Leonardi A. Vernal keratoconjunctivitis: pathogenesis and treatment. Prog Reti Eye Res 2002;21:319-39.
2. Alemayehu AM, Yibekal BT, Fekadu SA. Prevalence of vernal keratoconjunctivitis and its associated factors among children in Gambella town, southwest Ethiopia, June 2018. PLoS One 2019;14(4):e0215528.
3. Addis H, Jeng BH. Vernal keratoconjunctivitis. Clin Ophthalmol 2018;12:119–23.
4. Zicari AM, Capata G, Nebbioso M, De Castro G, Midulla F, Leonardi L, et al. Vernal Keratoconjunctivitis: an update focused on clinical grading system. Ital J Pediatr 2019;45(1):64.
5. La Rosa M, Lionetti E, Reibaldi M, Russo A, Longo A, Leonardi S, et al. Allergic conjunctivitis: a comprehensive review of the literature. Italian J Pediatr 2013;39:18.
6. Addis H, Jeng BH. Vernal keratoconjunctivitis. Clin Ophthalmol 2018;12:119–123.
7. Zicari AM, Mora B, Lollobrigida V, Occasi F, Cesoni MA, Megiorni F, et al. Immunogenetic investigation in vernal keratoconjunctivitis. Pediatr Allergy Immunol 2014;25(5):508–510.
8. holeva P, Tole D, Churchill A. Allergic eye disease in children: identifying the signs and symptoms. Int J Ophthalmic Practice 2014;5:50–52.
9. AlHarkan DH. Management of vernal keratoconjunctivitis in children in Saudi Arabia. Oman J Ophthalmol 2020;13(1):3-12.
10. Ahmad I, Rehman M, Khan J, Tahir Z. Comparison of efficacy of olopatidine hydrochloride 0.1% & ketotifen fumarate 0.025% in vernal keratoconjunctivitis. Ophthalmol Update 2015;13(4):254-257.
11. Hayilu D, Legesse K, Lakachew N, Asferaw M. Prevalence and associated factors of vernal keratoconjunctivitis among children in Gondar City, Northwest Ethiopia. BMC Ophthalmol 2016; 16:167.
12. Bacon AS, Ahluwalia P, Irani AM, Schwartz LB, Holgate ST, Church MK, et al. Tear and conjunctival changes during the allergen induced early and late phase response. J Allergy Clin Immunol 2000;106:948-54.
13. Khan MR, Azhar MN, Ansari MS, Arain TM, Qazi ZA. Comparison between topical olopatadine hydrochloride 0.1% and ketotifen fumarate 0.025% for the relief of symptoms of vernal kerato-conjunctivitis (VKC). Pak J Ophthalmol 2013; 29(4):202-205.
14. Kateralis CH, Ciprandi G, Missoten L, Turner FD, Bertin D, Berdeaux G. A comparison of the efficacy and tolerability of olopatadine hydrochloride 0.1% ophthalmic solution and cromolyn sodium 2% ophthalmic solution in seasonal allergic conjunctivitis. Clin Ther 2000; 24:1561–75.
15. Aguilar AJ. Comparative study of clinical efficacy and tolerance in seasonal allergic conjunctivitis management with 0.1% olopatadine hydrochloride versus 0.05% ketotifen fumarate. Acta Ophthalmol Scand 2000;78: 52–55.
16. Mantelli F, Santos MS, Petitti T, Sgrulletta R, Cortes M, Lambiase A, et al. Systematic review and meta-analysis of randomised clinical trials on topical treatments for vernal keratoconjunctivitis. Br J Ophthalmol 2007;91:1656-61.
17. Guest JF, Clegg JP, Smith AF. Health economic impact of olopatadine compared to branded and generic sodium cromoglycate in the treatment of seasonal allergic conjunctivitis in the UK. Curr Med Res Opin 2006;22:1777-85.
18. Leonardi A, Zafirakis P. Efficacy and comfort of olopatadine versus Ketotifen ophthalmic solutions: a double-masked, environmental study of patient preference. Curr Med Res Opin 2004;20(8): 1167–1173.