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Comparative Efficacy and Safety of Topical Cyclosporine, Dexamethasone and Loteprednol in Vernal Keratoconjunctivitis

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ABSTRACT

Introduction: Vernal keratoconjunctivitis is a chronic, severe, recurrent and bilateral seasonal allergic conjunctivitis causing vision threatening complications for which drugs like topical corticosteroids and cyclosporine are required for severe inflammation.

Aims &Objectives: To compare the efficacy and safety of topical cyclosporine, dexamethasone and loteprednol in vernal keratoconjunctivitis.

Place and Duration of Study: Department of Ophthalmology, Shaikh Zayed Hospital, Lahore from 1st December 2019 to 30th June 2020.

Materials & Methods: A randomized controlled trial in which one hundred and fifty patients of VKC (vernal keratoconjunctivitis) were enrolled in which 50 were from cyclosporine group, 50 were from dexamethasone group and 50 were from loteprednol group. Detailed ocular and systemic histories were recorded followed by ocular examination including recording of visual acuity, intraocular pressure (IOP) measurements, slit lamp examination of anterior segment and fundoscopy.

Results: The mean ages of the patients were 18.12±7.76 years, 17.02±7.22 years and 17.50±7.22 years in cyclosporine, dexamethasone and loteprednol groups respectively. At 1st week, in cyclosporine, dexamethasone and loteprednol groups the mean intraocular pressures of patients were 16.09±1.44 mmHg, 16.39±1.37 mmHg and 16.69±1.46 mmHg respectively (P=0.114). Similarly at 6th months follow-up in cyclosporine, dexamethasone and loteprednol groups, the mean intraocular pressure of patients was 16.09±1.44 mmHg, 17.26±1.13 mmHg and 16.67±1.44 mmHg respectively (P=0.000). Posterior subcapsular opacity of lens was observed in one case in dexamethasone group while in both other groups no posterior subcapsular opacity of lens occurred.

Conclusion: Cyclosporine is a safe and effective drug as compared to dexamethasone and loteprednol in treating vernal keratoconjunctivitis.

Key words: Dexamethasone, Cyclosporine, Loteprednol, Vernal keratoconjunctivitis

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is the condition observed essentially in hot, dry and windy atmospheres most generally in Central and West Africa and Mediterranean regions.[1,2] It is additionally observed normally in Japan, Middle East, India, South and North America. Allergic conjunctivitis is usually underdiagnosed and not treated timely. Better understanding is provided by the researchers about the inflammatory cells, mediators, and immunologic events involved in pathogenesis of ocular allergy. Several allergic disorders are caused by epithelial barrier dysfunction. Breach in epithelial barrier causes allergens and pathogens to gain access to the underlying connective tissue, initiating a strong immune response due to recognition of pathogens by epithelial receptors and the immune cells (mast cells and macrophages). Furthermore sensitization and activation of immune response leads to type 2 inflammatory reaction which is a characteristic feature of the allergic disorders.[3,4] VKC is responsible for 0.1–0.5% of all ocular diseases in developed world. In Europe, the prevalence of VKC is approximately 1.2–10.6 cases per 10000. Its frequency increases in warm and dry tropical and sub-tropical countries of The Middle East, Africa, Asia and Latin America.[5] Most of VKC is seen in patients between 5-25 years of age with a time of beginning between 9-12 years of age.[6]

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In VKC cases, irritation is caused by immunoglobulin E mediated type I hypersensitivity reaction and penetration of eosinophils/lymphocytes results from type IV hypersensitivity. The major findings clinically are papillae on the upper tarsus, edema and trantas dots at limbus and shield ulcer on cornea.[7] Vernal keratoconjunctivitis is a chronic, severe, recurrent and bilateral seasonal allergic conjunctivitis which is described by itching, photophobia, foreign-body sensation, lacrimation, redness and ropy discharge. It may be associated with other atopic manifestation like eczema, hay fever, allergic rhinitis and allergy of food.[6] It can take one of the three forms; palpebral, bulbar and mixed. The bulbar one is with Horner Trantas nodules and limbal edema and the palpebral form is with conjunctival hyperemia and diffuse papillary hypertrophy on superior tarsal surface. Both forms may also coexist. Chronic eye rubbing has the potential to induce keratoconus, keratitis, shield ulcer, astigmatism and corneal hydrops.[8] Vernal keratoconjunctivitis is dealt effectively with conservative measures like cold packs, dark glasses and pharmacologic treatment with topical anti-allergy drugs (topical vasoconstrictors, topical antihistamine/mast cell stabilizers), and artificial tears for management of mild-to-moderate form of VKC.[9] The patient is told to avoid the natural and synthetic operators that are known to incite the process.[10] VKC can induce chronic debilitating symptoms along with tissue destruction. Topical non-steroidal anti-inflammatory medications can be utilized to relieve signs and symptoms.[11,12]. Corticosteroids are considered as the primary therapy for acute uveitis not associated with infection. Steroids can be given by different routes, in addition to uveitis role of steroids is also important in the treatment of inflammatory conditions of conjunctiva. [13] Loteprednol etabonate 0.5% is a weak topical steroid as compared to topical Dexamethasone 0.1% with less hazard for raising IOP. It ought to be considered as a possibility for patients who require long haul corticosteroid therapy.[14]. Tacrolimus 0.1% eye drops is considered safe and beneficial in the treatment of vernal keratoconjunctivitis especially tarsal form involving palpebral conjunctiva. Topical Tacrolimus improves symptoms and decreases hyperplasia of papillae .[15] Topical cyclosporine 0.05% is an immunomodulatory agent that improves tear film and limits inflammation of ocular surface. Different studies showed that topical cyclosporine has excellent results in cases of moderate and severe dry eyes and its efficacy is evaluated for improvement of clinical features of ocular surface diseases. .[16] It is proved in studies that calcineurin inhibitor reduces inflammation by inhibiting T-cell activity. This mechanism is quite different from steroids.[17] Corticosteroids are also considered effective in ocular inflammatory diseases. Combination therapy in the form of topical steroids and non-steroidal anti-inflammatory drugs has been used in many inflammatory ocular conditions. [18] It has been repeatedly studied as a treatment modality for dry eye. It is available in 0.05-2% concentration. The ocular and systemic undesirable effects are minimal as compared to steroids.[19] Topical olopatadine 0.2% is an antihistamine used in a dose of BD (twice a day) as an adjunctive therapy in VKC. The rationale of our study is to prove the effectiveness of topical immunosuppressants in the treatment of VKC as an alternative to conventional topical steroids.

MATERIALS AND METHODS

This randomized controlled study was done at Department of Ophthalmology, Shaikh Zayed Hospital Lahore from 1st December 2019 to 30th June 2020 after the approval of Ethical committee (3639/M.D/2020 dated 04-12-20). One hundred and fifty patients of VKC were enrolled and divided into three random groups by non-probability sampling (50 in each group). Group A received Loteprednol 0.5% eye drops as QID dosage for 2 weeks and tapered to BID dosage over the next 6 weeks and topical Olopatadine 0.5% eye drops BID, Group B patients were given treatment with topical Cyclosporine 0.05% BID for 6 weeks and topical Olopatadine 0.5% BID, Group C patients were given Dexamethasone 0.1% eye drops QID for 2 weeks and tapered to BID over the next 6 weeks and topical Olopatadine 0.5% BID. Both males and females, age 5-30 years and symptoms and signs suggestive of VKC were included. Allergic conjunctivitis due to atopy and VKC patients using contact lenses were excluded. Detailed ocular and systemic histories were recorded followed by ocular examination including measurement of visual acuity, intraocular pressure, slit lamp examination and fundoscopy. All patients were followed for a period of 3-6 months and clinical findings were recorded. All the collected data was entered and analyzed by using the SPSS-22. Comparison between groups was made by using student's 't' test. $P<0.05$ is considered significant.

RESULTS

The mean ages were17.50±7.22 years in group A ,18.12±7.75 years in group B and 17.02±7.22 years in group C (Table.1). According to gender, 25 males and 25 females were in group A, 21 males and 29

females in group B and 22 males and 28 females in group C. In group A, 27 patients had mild VKC grading and 23 had moderate grading. In group B, 34 patients had mild VKC grading and 16 had moderate grading. In group C, 31 patients had mild VKC grading and 19 had moderate grading. 28 patients had itching in group A, 26 patients had itching in group B, and 34 had itching in group C. The watering was noted in 26 patients in group A, 22 patients in group B, 19 patients in group C. 27 patients had discharge in group A, 19 patients in group B, 34 patients in group C.

Table 1: Frequency distribution of gender in all groups

Gender	Study Groups			Total
	Loteprednol A	Cyclosporine B	Dexamethasone C	
Male	25	21	22	68
Female	25	29	28	82
Total	50	50	50	150

The redness in eyes were noted in 25 patients in group A, 25 patients in group B, 27 patients in group C. The photophobia was noted in 25 patients in group A, 24 patients in group B, 26 patients in group C. There was ocular pain in 30 patients in group A, 29 patients in group B, 20 patients in group C. The burning sensation was noted in 15 patients in group A, 27 patients in group B, 22 patients in group C. The pricking sensation was noted in 24 patients in group A, 25 patients in group B, 22 patients in group C. The lid swelling was observed in 31 patients in group A, 26 patients in group B, 28 patients in group C. In group A, 15 patients had limbal VKC, 13 patients had palpebral VKC and 19 patients had mixed VKC. There was limbal VKC in 35 patients, palpebral VKC in zero and mixed VKC in 15 patients in group B, 25 patients had limbal VKC, 12 patients had palpebral VKC and 13 patients had mixed VKC in group C. Table 2.

Table 2: Distribution of clinical features of VKC in all groups (n=150)

Variable	Loteprednol group A	Cyclosporine group B	Dexamethasone group C
VKC Grading			
Mild	27	34	31
Moderate	23	16	19
Itching			
Yes	28	26	34
No	22	24	16
Watering			
Yes	26	22	19
No	24	28	31
Discharge			
Yes	27	19	34
No	23	31	16
Redness			
Yes	25	25	27
No	25	25	23
Photophobia			
Yes	25	24	26
No	25	26	24
Ocular of Pain			
Yes	30	29	20
No	20	21	30
Burning sensation			
Yes	15	27	22
No	35	23	28
Pricking sensation			
Yes	24	25	22
No	26	25	28
Lid swelling			
Yes	31	26	28
No	19	24	22
Limbal VKC			
Yes	12	35	25
No	38	15	25
Palpebral VKC			
Yes	19	-	12
No	31	35	38
Mixed VKC			
Yes	19	15	13
No	31	35	37

At 1st week follow-up, in left eyes, the mean IOP was 16.69±1.46 mmHg in group A ,16.09±1.44 mmHg in group B and 16.39±1.37 mmHg in group C. Statistically insignificant (P=0.114) difference was observed. In right eyes, the mean IOP was 16.61±1.43 mmHg in group A, 15.99±1.44 mmHg in group B and 16.30±1.28 mmHg in group C and Statistically insignificant (P=0.086) difference was observed (Table 3).

Table 3: Comparison of IOP in all groups at 1st week follow-up

IOP (mmHg)	Loteprednol group	Cyclosporine group	Dexamethasone group	P value
Left	16.69±1.46	16.09±1.44	16.39±1.37	0.12
Right	16.61±1.43	15.99±1.44	16.30±1.28	0.09

At 1st month follow-up, in left eyes, the mean IOP was 16.68±1.45 mmHg in group A ,16.09±1.44 mmHg in group B and 16.09±1.14 mmHg in group C. Statistically insignificant (P=0.044) difference was observed. In right eyes, the mean IOP was 16.61±1.41 mmHg in group A ,15.99±1.19 mmHg in group B and 15.91±1.12 mmHg in group C. Statistically insignificant (P=0.018) difference was observed (Table 4).

Table 4: Comparison of IOP in all groups at 1st month follow-up

IOP (mmHg)	Loteprednol group A	Cyclosporine group B	Dexamethasone group C	P value
Left	16.68±1.45	16.09±1.44	16.09±1.14	0.044
Right	16.61±1.41	15.99±1.19	15.91±1.12	0.018

At 3rd month follow-up, in left eyes, the mean IOP was 16.68±1.45 mmHg in group A, 16.09±1.44 mmHg in group B and 17.34±1.73 mmHg in group C. Statistically significant (P=0.000) difference was observed. In right eyes, the mean IOP was 16.61±1.41 mmHg in group A, 15.99±1.44 mmHg in group B and 17.19±1.69 mmHg in group C. Statistically significant (P=0.001) difference was observed (Table 5).

Table 5: Comparison of IOP in all groups at 3rd month follow-up

IOP (mmHg)	Loteprednol group A	Cyclosporine group B	Dexamethasone group C	P value
Left	16.68±1.45	16.09±1.44	17.34±1.73	0.000
Right	16.61±1.41	15.99±1.44	17.19±1.69	0.000

At 6th month follow-up, in left eyes, the mean IOP was 16.67±1.44 mmHg in group A, 16.09±1.44 mmHg in group B and 17.26±1.13 mmHg in group C. Statistically significant (P=0.000) difference was observed. In right eyes, the mean IOP was and 16.60±1.39 mmHg in group A, 15.99±1.44 mmHg in group B and17.17±1.19 mmHg in group C. Statistically significant (P=0.000) difference was observed (Table 6).

Table 6: Comparison of IOP in all groups at 6th month follow-up

IOP (mmHg)	Loteprednol group A	Cyclosporine group B	Dexamethasone group C	P value
Left	16.67±1.42	16.09±1.44	17.26±1.14	0.000
Right	16.60±1.42	15.99±1.44	17.17±1.19	0.000

DISCUSSION

VKC is a severe type of allergic ocular disease . It has more exacerbations during summer and spring seasons. Conventional anti histamine and topical steroid therapy for allergic conjunctivitis is generally not sufficient. Delayed treatment of VKC can lead to irreversible visual loss so timely diagnosis and proper treatment is very important. It more particularly affects the children and young adults.[20-21]. Use of topical and systemic corticosteroids is associated with development of cataract and glaucoma. [22]Topical corticosteroids are very well-known to be the most effective medication for treatment of VKC. Vernal keratoconjunctivitis (VKC) is usually underdiagnosed and remains untreated ocular surface disease so limited epidemiological data is available in Asia. Treatment of VKC should involve a systematic approach which includes identifying etiological and trigger factors, patients awareness on ophthalmic diseases, and explaining clinical features. In a new era of treatment modalities, the use of topical cyclosporin should be started on early basis to treat the inflammatory process and complications of VKC, with topical use of corticosteroids as an add-on, short-pulse treatment for chronic cases and during acute exacerbations .[23-24] It is also associated with many other atopic exhibitions in about 50% of the patients. The occurrence of VKC has also been increased in cooler areas, may be because of movement of people from vulnerable populations. The pathological events of VKC are still not very clear and it is not possible to identify any single pathological process responsible for underlying chronic ocular inflammation. Hypothesis of different studies show that both autoimmune and allergic mechanism play an important role. Oxidative stress also contributes significantly to the pathological sequence of the disease[19, 20,] The lack of specific biomarkers of the disease makes the treatment very difficult. The standard treatment of VKC includes use of topical mast cell stabilizers, non-steroidal anti-inflammatory drugs and immunosuppressant drugs. Modern therapies are still under investigation.[25] Steroids are very effective in controlling both acute and chronic episodes of disease. However, the long-term complications of topical corticosteroid should be monitored. Immunomodulator drugs such as tacrolimus and cyclosporine can be used as steroid-sparing agents.[26] There are several therapeutic options available for the management of VKC. These include topical steroids, mast-cell stabilizers, antihistamines and topical non-steroidal anti-inflammatory agents. Topical mast-cell stabilizers are considered as one the major methods for treatment of VKC as they exhibit least adverse effects. Among all the mast-cell stabilizers, lodoxamide is a successful medicine to control the initial phase of inflammatory process of VKC and improving severe signs and symptoms of vision disruption. Lodoxamide acts by stabilizing the mast cell membrane from degranulation and inhibiting the release of intracellular histamine .[27]

There were significantly higher levels of IOP observed with dexamethasone as compared to other drugs. Loteprednol also showed mild change in IOP level during 6 months course. So, both steroids can cause a change in IOP level during their use and dexamethasone is more effective in the development of cataract or glaucoma. In our study cataract was

observed in one case in dexamethasone group while in other both groups, no cataract occurred.

In one double-blinded trial, De Smedt et al evaluated few patients of VKC in Rwanda and observed no significant differences between 2% topical cyclosporine and 0.1% dexamethasone in terms of efficacy for the management of acute VKC. After about one month of treatment, the reductions in clinical score and improvement in the visual acuity were comparable in both drugs, but the foreign body sensation was more pronounced with topical cyclosporine.[28] Central Africa and Willen, Christi et al reported that there was statistically insignificant difference between the treatment groups.[29] Studies on the use of 1-2% topical cyclosporine in keratoconjunctivitis sicca have already been available during last two decades.[28-30] This study is based on current practices in the treatment of VKC thus making it possible to solve many problems and challenges in the treatment, such as the proper dosage of topical cyclosporine in children facing difficulty instilling 4 drops per day during school timings. This study shows comparison of efficacy of different dosages of 2% and 0.1%. .[30] A study by Neri Pucci et al presented that the cyclosporine eye-drops are effective and harmless to cure severe VKC, while no major side effects were observed in any patient. In most of the cases, therapeutic effects were attained after two weeks of treatment. The therapeutic effects were initially maintained during the following three months with slow reduction in symptoms.[32] Arkendu Chatterjee et al reported that topical 0.05% cyclosporine is an effective and harmless drug for management of patients with moderate to severe VKC with good steroid-cautious effects.[33] Daniell et al [34] and Ozlem et al [36] found that cyclosporine had no serious adverse effects for example there was no increase in IOP in any study.

Many trials observed that topical use of 2% cyclosporine is a beneficial treatment for VKC. It reduces the need of additional topical steroids application.[37-38] In one double-blinded, placebo-controlled trial, 2% cyclosporine was applied in 24 children to treat severe VKC. In most of the cases, the effects of 2% topical cyclosporine on ocular surface were achieved after two weeks of its application.[31] Clinical studies of 0.05% cyclosporine topical preparation in patients with dry eye syndrome showed marked improvement of symptoms. A study conducted in Korea enrolling 392 patients with signs and symptoms of dry eye syndrome showed that most (72%) patients were satisfied with topical cyclosporine treatment. Symptoms of dry eye and Schirmer's test scores showed improvement over the three-month study period. However few side effects were noted in the study like mild ocular discomfort and ocular itching.[35] Bonini et al reported that the incidence of glaucoma induced by topical steroids is only 2% with prolonged use of steroids.[20] Steroids are commonly used drugs for various allergic and inflammatory ocular conditions. Despite many benefits of topical steroids in many inflammatory and allergic ocular diseases, prolonged topical steroid usage has many ocular side effects , the most important being glaucoma and cataract.[38] This is a seasonal problem and will recur every year as the same season will arrive. On the basis of findings of this study, we can rely and strongly recommend using the topical cyclosporine instead of prescribing topical steroids. Dexamethasone can cause cataract or glaucoma in early treatment phase. Loteprednol seems to be safe during first few months, but its prolonged use may also cause glaucoma and cataract, so topical cyclosporine can be safer and more effective than topical steroids.

CONCLUSION

Cyclosporine can be safe and effective as compared to dexamethasone and loteprednol for the treatment of VKC. So, cyclosporine can be a good alternative to dexamethasone without comprising the ocular health of the patients and can be prescribed as a primary therapy for future use. VKC is a seasonal problem and recur every year and repeatedly forever requiring prolonged topical treatment. It is better to prescribe topical cyclosporine instead of other topical steroids, as their prolonged use can cause damage to eye tissues and associated with high risk of glaucoma and cataract.

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