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Clinical study of role of topical tacrolimus 0.03% eye ointment in vernal keratoconjunctivitis

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Abstract
Background: Vernal keratoconjunctivitis (VKC) is recurrent bilateral allergic inflammation of conjunctiva and cornea. It is more prevalent in hot dry climate like Indian subcontinent. Antihistaminics and mast cell stabilizers are the first line treatment of VKC. In severe cases corticosteroids are used. But because of severe side effect of steroids immunomodulators have been used as substitutes for corticosteroids. The aim of this study is to determine the clinical efficacy of topical 0.03% tacrolimus as a sole therapy in VKC.
Material and methods: 50 patients of VKC were selected & divided into two subgroup.
Group A: In which 0.03% tacrolimus ointment was applied twice a day with tear drops as placebo.
Group B: In which 0.1% olapatadine ophthalmic solution was applied twice a day along with 0.03% tacrolimus ointment. Each patient was examined on slit lamp and symptom and sign was graded on a scale from 0 to 3 before the introduction of therapy, on day 7, 30 and 90. The student's T-test for independent sample was used to compare the results between two groups.
Results: There is significant reduction in the signs (conjunctival hyperaemia, tarsal papillary reaction, punctuate epithelial keratitis, limbal gelatinous infilterate) and symptoms (itching, tearing, foreign body sensation, photophobia, discharge) in both the group on day 7, 30 and 90 days. ($P<0.05$)
Conclusion: The isolated use of tacrolimus and the combined use of tacrolimus with olopatadine have similar efficacy in reducing clinical symptoms and signs in cases of VKC which are refractory to conventional therapy.

Keywords: Vernal keratoconjunctivitis, tacrolimus, immunomodulators, olopatadine

Introduction

Allergic eye disease has been considered as a common ocular condition encountered in clinical practice. Vernal keratoconjunctivitis (VKC) is recurrent, bilateral interstitial, self-limiting, allergic inflammation of the conjunctiva having a periodic seasonal incidence which subsequently affects cornea. Worldwide the incidence of VKC has been reported in most of the continents. Indian population is also significantly present with VKC [1, 2].

Reports indicate the wide variation in prevalence, severity, course of the disease and treatment response. As per various studies this condition is more prevalent in hot, dry climatic zone [2].

VKC differs from seasonal allergic conjunctivitis and perennial allergic conjunctivitis because it is a condition mediated by Th2 lymphocytes. However, the precise roles of mast cells, eosinophils, fibroblasts, and their cytokines in the inflammatory process and the remodelling of conjunctival tissue remain poorly established [3-5].

The topical use of antihistamines, mast cell stabilizers (MCSs), and, more recently, drugs with both effects, termed dual-action drugs (DADs), represent the first-line treatment for VKC. In the more severe forms, corticosteroids are used for a short period to induce the remission of the allergic crisis. However, there are cases where it is not possible to withdraw the corticosteroid without any clinical worsening, thus leaving patients susceptible to risks caused by the prolonged use of these drugs, such as cataract, glaucoma, and corneal complications. For the past two decades, immunomodulators have been used as substitutes for corticosteroids in allergic crisis control and the maintenance of asymptomatic VKC patients [6].

Tacrolimus, a macrolide derived from the bacterium Streptomyces tsukubaensis, is a potent immunomodulator capable of decreasing the production of inflammatory mediators by T lymphocytes through the inhibition of calcineurin, an intracytoplasmic protein essential for interleukin (IL)-2 and IL-4 transcription [7, 8].

There are numerous reports of the successful use of tacrolimus for the treatment of autoimmune diseases of the ocular surface, such as dry eye, scleritis, Mooren ulcer, cicatricial conjunctivitis, atopic, and VKC [9-13]. Recent clinical trials have also shown that, like corticosteroids, tacrolimus and other immunosuppressive drugs have similar efficacy in allergic crisis control and maintenance therapy for VKC but with a low incidence of side effects [14-16].

This study is focused on determining the efficacy of Tacrolimus- as a sole therapy in VKC. A group of patients with characteristic features of VKC coming in department of pediatric ophthalmology & strabismus at a tertiary eye care centre located in Rajasthan, India will be studied. As this region is with hot, windy and dry climatic condition, the prevalence of VKC is higher over here.

Material and methods

The study group consisted of all VKC patients refractory to conventional therapy coming in the out-patient department at a tertiary eye hospital. Refractory, in this context, meant that the

clinical condition was maintained or worsened during the use of topical corticosteroids or that there was a relapse after withdrawal. Randomly 50 patients were selected & divided into two subgroups A and B consisting of 25 each.

Group A (Experimental Group): In which 0.03% tacrolimus ointment was applied twice a day with tear drops as placebo.
Group B (Control Group): In which 0.1% olapatadine ophthalmic solution was applied twice a day along with 0.03% tacrolimus ointment.
Both eye drops had similar flasks, with no identification and were given to the patients together with the ointment. For double masking of the study, the eye drop flasks were numbered and contained no identification of the drug. The content of the flasks was only revealed after the end of the data collection period. The randomization was performed using a block system.
Each patient was examined on slit lamp and each symptom and sign was graded on a scale from 0 to 3 (Table 1 and Table 2). The symptoms and signs were assessed before the introduction of therapy, after 30 days and after 90 days.
Clinical impression of the progress of each case and the self-provided by the patient will be noted using an objective 0 to 3 scale. To assess the safety and side effects of the treatment, itching, burning, intraocular pressure, lens opacification, secondary infections, or other possible complications were assessed.
The Institutional Ethics Committee on Human Subjects Research, 2014-15, granted approval, subsequent to which data collection for the study was initiated. The Student's *T* test for independent samples was used. To compare the results for the two assessment times, within each group, the Student *T* test for paired samples was used. When comparing the 2 groups regarding the qualitative variables, Fisher exact test and the chi-square test were used. *P*-values less than 0.05 were considered significant. The statistical software, statistical product and service solutions (SPSS 15.0) was used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables, etc.

Results

In the study group the age of the patients were ranging from 6 to 20 years. Majority of the patients were found between 6 years to 15 years. 41 out of 50 (82.0%) were male and 09 (18.0%) were female. Large numbers of patients were of school going children (82.0%) followed by preschool children (12%) and working outdoors with their parents (6%). Most of the patients were from rural area (80.0%). Majority of the patients were of bulbar variety (46.0%) of VKC followed by palpebral (34.0%) and mixed (20%). Total 11 out of 50 (22%) patients were presented with corneal involvement in which three out of twenty three (13.04%) cases were of bulbar form, four out of seventeen (23.52%) cases were of palpebral form and four out of ten (40.00%) cases were of mixed form shows corneal involvement. Superficial punctate keratitis in seven cases and epithelial scarring in four cases were observed. Corneal involvement was observed more among patients having palpebral or mixed type of disease.

Result of therapeutic trial with drugs

50 patients were divided into two groups and symptoms & signs were assessed on day 0 (base line) and at day 7, day 30, day 90. Mean scores of symptoms (itching, tearing, foreign body sensation, photophobia, discharge) and signs (conjunctival hyperaemia, tarsal papillary reaction, punctuate epithelial keratitis, limbal gelatinous infilterate) and their comparision in between two groups with p value are summarised in table-3
Allergic eye disease has been considered as a common ocular condition encountered in clinical practice. Vernal keratoconjunctivitis (VKC) is recurrent, bilateral interstitial, self-limiting, allergic inflammation of the conjunctiva having a periodic seasonal incidence which subsequently affects cornea. Worldwide the incidence of VKC has been reported in most of the continents. Indian population is also significantly present with VKC [1, 2].
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VKC differs from seasonal allergic conjunctivitis and perennial allergic conjunctivitis because it is a condition mediated by Th2 lymphocytes. However, the precise roles of mast cells, eosinophils, fibroblasts, and their cytokines in the inflammatory process and the remodelling of conjunctival tissue remain poorly established [3-5].
The topical use of antihistamines, mast cell stabilizers (MCSs), and, more recently, drugs with both effects, termed dual-action drugs (DADs), represent the first-line treatment for VKC. In the more severe forms, corticosteroids are used for a short period to induce the remission of the allergic crisis. However, there are cases where it is not possible to withdraw the corticosteroid without any clinical worsening, thus leaving patients susceptible to risks caused by the prolonged use of these drugs, such as cataract, glaucoma, and corneal complications. For the past two decades, immunomodulators have been used as substitutes for corticosteroids in allergic crisis control and the maintenance of asymptomatic VKC patients [6]. Tacrolimus, a macrolide derived from the bacterium Streptomyces tsukubaensis, is a potent im
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