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Role of sirolimus topical application in recalcitrant cases of vernal keratoconjuctivitis

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Abstract

Aim: To study the role of sirolimus topical application (0.03% and 0>1% concentration) in recalcitrant cases of vernal keratoconjuctivitis in the region of Bikaner, Rajasthan.

Materials & Methods: After patient selection of suspected vernal keratoconjuctivitis sociodemographic data risk factors and clinical symptoms were recorded. Ophthalmic examination was performed including records details of symptoms, drugs used, visual acuity, intraocular pressure measurement slit lamp examination. Patients categorized according symptoms and prepared sirolimus eye drop prescribed to patient in two groups and follow up done in every 15 day for 3 month

Results: Male preponderance was seen in the ratio 3.17:1. 68% cases were students followed by 20% cases involved in outdoor activity. All the cases were bilateral and most of seen in the summer month of April-June i.e. 42%. 100% improvement in itching, redness, watering, ropy discharge, photophobia and in corneal involvement than conjunctival hyperemia, papillary hypertrophy, gelatinous ring around limbus and cobblestone lesion have less improvement. 0.1% sirolimus e/d have faster action than 0.03%

Conclusion: Sirolimus eye drop is effective and sare therapy for recalcitrant cases of vernal keratoconjunctivitis. Both concentrations of sirolimus are effective and safe but 0.1% has faster action than 0.03%. Higher concentration (0.1%) used in severe cases for 30 days followed by lower concentration (0.03%). Sirolimus eye drop is alternate of steroid drop for long term use.

Keywords: Vernal keratoconjunctivitis, Sirolimus, topical, recalcitrant cases.

1. Introduction

Vernal keratoconjunctivitis is bilateral recurrent external ocular inflammatory disorders of the conjunctiva and cornea. It is also known spring catarrh. It is allergic disorder in which IgE and T helper lymphocyte play an important role in mechanism. It is sporadic and non contagious.

Three clinical types are seen (1) Papillary Vernal keratoconjunctivitis shows papillary hypertrophy (2) Limbal is present with burning, itching, lacrimation, foreign body sensation and photophobia (3) Mixed. The aetiology of vernal keratoconjunctivitis includes heat, humidity, and light, disturbance of endocrinal gland function, seasonal allergy. Aetiopathogenesis is not clear but present knowledge of immunopathogenesis of Vernal keratoconjunctivitis involve three main factors: (1) CD-4 T cells derived cytokines IL-4 and IL-13 which are responsible for IgE production from B lymphocyte which play a major role in pathogenesis.(2) Mast cell release proinflammatory mediator (histamine, leukotrine, prostaglandin D_2, cathepsin G) which are responsible for symptoms and pathological changes in conjunctiva.(3) Increase level of adhesive molecules[1].

Diagnosis is made on the basis of clinical symptoms and sign. Treatment can be given by topical or injectable route. In topical route we can use levocabastine (0.05%), flurbiprofen (0.3%), ketorolac (0.5%), olopatadine (0.1%), dexamethasone (0.1%), prednisolone (0.1%), mitoomycin-c, topical cyclosporine, topical tacrolimus and in injectble route (subconjunctival) triamcilone acetonide are used. Sirolimus is immunosuppressive which used for reduse activity of immune system in patient of organ transplant. In patient of vernal keratoconjunctivitis we used steroid which long term use have many side effects. So as an ophthalmologist we are in search of a drug which replace steroid in treatment of vernal keratoconjunctivitis devoid of any major side effects.

2. Materials and Methods

The study was conducted in 50 patient of either sex and any age suffering from vernal keratoconjunctivitis attending the out-door in Department of Ophthalmology, S.P. Medical College and associated group of hospitals, Bikaner and undergone complete clinical evaluation and complete ophthalmic examination and treated under treatment protocol.

2.1 Patient selection

Patient with vernal keratoconjunctivitis presenting in ophthalmology outdoor at S.P. Medical College and associated group of hospitals, Bikaner in 2006 included in the study. Patient were recorded and divided in four grade according to severity of symptoms (like itching, watering, redness, ropy discharge and photophobia) and ocular clinical sign (bulbar hyperemia, palpebral papillae, corneal limbal oedema and superficial punctuate keratopathy)

2.2 Clinical procedure

50 patient of vernal keratoconjunctivitis were taken and divided into two groups

Groups	Concentration Topical sirolimus	Number of Patients	Dosage
I	0.03%sirolimus eye drop	25	Twice daily
II	0.1%sirolimus eye drop	25	Once daily

Complete Blood Count (CBC), Blood urea nitrogen (BUN), Creatinine, Serum Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT) were recorded at the start of treatment and subsequently at the end of follow up period of three months. Patient were be followed up every 15 days for 3 months and improvement in sign and symptoms were recorded and graded

Preparation of sirolimus drop from 1mg tablet of sirolimus was dissolved in ocular lubricant containing hydroxyl propyl methyl cellulose 2%, sodium chloride 0.49%, potassium chloride 0.075%, calcium chloride 0.048%, magnesium chloride 0.030%, sodium citrate 0.17% and water under complete aseptic condition. For 0.1% concentration drop 1mg tablet dissolve in 1ml and for 0.03% concentration 1mg tablet dissolve in 3ml.

3. Results

Our observation are based on 3 months follow up study of 50 patients diagnosed as cases of recalcitrant vernal keratoconjunctivitis from department of ophthalmology, S.P. Medical College and associated group of hospitals, Bikaner. The patients were divided into two groups 25 in each group. The first group was given 0.03% sirolimus eye drop and the second group was given 0.1% sirolimus eye drop. Out of 50 patient 38(76%) were male and 12(24%) were female. The overall male to female ratio was 3.17:1.

Maximum patients were from age group 5-10 yrs (32%) followed by 16-20 yrs (30%). Mean age group in group I was 13.28 and in group II was 15.84 years (Fig. 1)

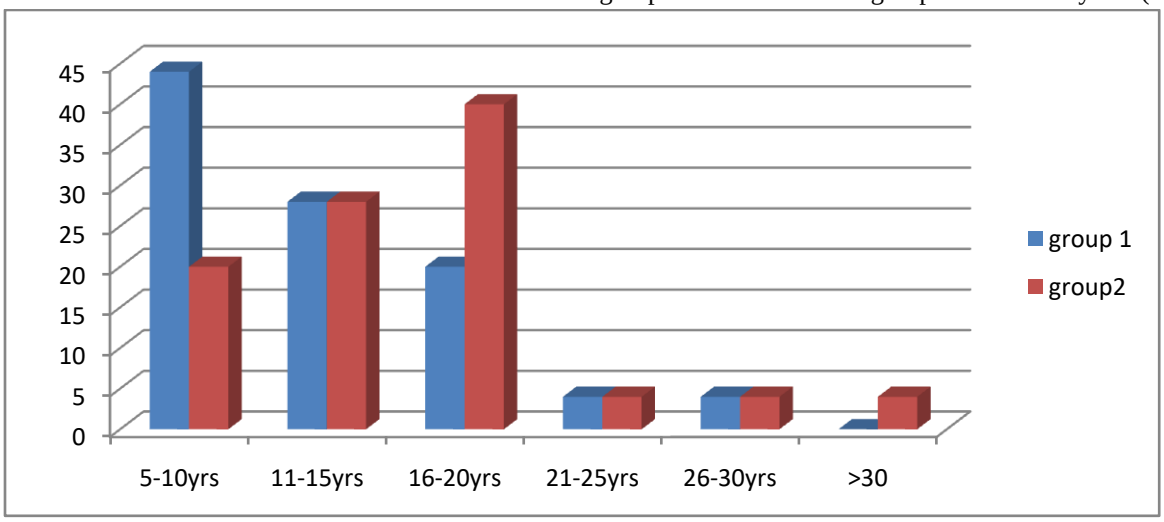


Figure 1: Age distribution in percentage in vernal keratoconjunctivitis group

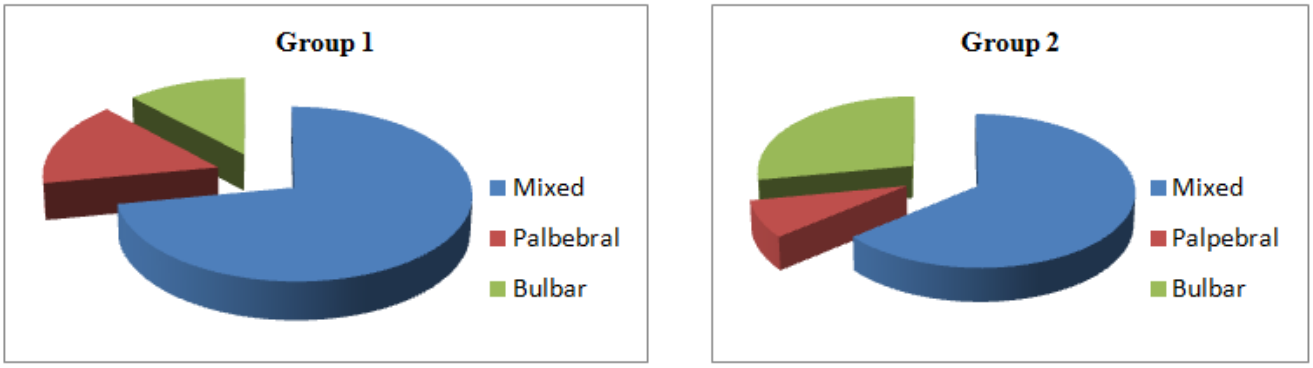
Table 1: Disease was more common in students followed by patients having outdoor activity

Occupation	Group I(n=25)		Group II(n=25)		Total(n=50)	
	No.	%	No.	%	No.	%
Student	19	76	15	60	34	68
Outdoor	4	16	6	24	10	20
Indoor	2	8	4	16	6	12

Disease was most common in summer months of April- June in all the two groups. The next common season was July to September. The disease was bilateral in all the two groups.

Family or personal history of atopy was negative in all patients in both groups. The mixed form was more common in two groups i.e. 68%; bulbar form was 20% and palpebral form was 12 % (Figure 2). There is no significant difference in two groups (x^2=2.3843; p>0.05 NS)

Figure 2:



Symptoms of itching, watering and redness were present in all cases. Photophoia was present in 70% cases and ropy discharge was seen in 44% cases. No statistical significant difference in the two groups (p=>0.05%).

Sign in cases of vernal keratoconjunctivitis in two groups shows no statistical significant difference in the two groups (p=>0.05%) (Table 2).

Table 2: Sign in vernal keratoconjunctivitis

Sign	Group I		Group II		Total	
	No.	%	No.	%	No.	%
Conjunctival hyperemia	50	100	50	100	100	100
Gelatinous ring around limbus	42	84	46	92	88	88
Papillary hypertrophy at superior tarsus	44	88	38	76	82	82
Mucoid nodules around limbus	24	48	26	52	50	50
Cobblestone lesions	6	12	12	24	18	18
Corneal involvement	2	4	6	12	8	8

Table 3: Improvement in sign with treatment

Clinical sign	Group	Percentage improvement on follow up days						
		7^{th} day	15^{th} day	30^{th} day	45^{th} day	60^{th} Day	75^{th} day	90^{th} Day
Conjunctival hyperemia	I	0	0	0	4	76	96	100
	II	0	0	24	60	92	100	100
Gelatinous ring around limbus	I	16	16	16	20	76	96	100
	II	8	8	28	92	100	100	100
Papillary hypertrophy	I	12	12	12	16	80	96	100
	II	36	36	56	80	96	100	100
Cobblestone lesions	I	88	88	88	92	100	100	100
	II	72	72	80	88	100	100	100
Corneal involvement	I	96	96	100	100	100	100	100
	II	88	88	92	96	100	100	100

Percentage improvement in clinical sign

In new clinical sign ptosis found in one patient, keratinisation of palpebral conjunctiva found in 12 patient and palpebral conjunctival pigmentation found in 22 patient. After end of treatment only ptosis in improved, keratinisation of palpebral conjunctiva and conjunctival fornix pigmentation remained unchanged.

Improvement in symptoms (itching, redness, watering, photophobia and ropy discharge) was 0% in initial two follow up (7^{th} day and 15^{th} day). Improvement was noted 100% in all symptoms in last three follow up (60, 75 and 90 day follow up). There was highly significant decrease in symptoms (p=<0.001).

Side effects seen were heaviness/ swelling in upper lid in both groups after drug instillation in 4% cases.

There was no change in the different investigation values at 0 visit and the investigation values at the end of three month of follow up.

4. Discussion

The present study was conducted to evaluate the efficacy and safety of 0.03% and 0.1% sirolimus eye drop in recalcitrant vernal keratoconjunctivitis 50 cases which are devided into two groups (each 25) in department of ophthalmology, S.P. Medical College and associated group of hospitals, Bikaner

It is almost universally found that a very high percentage of cases are male: Saemisch [2] 79%; Togby[3] 79.7%; Biegelman[4] 77.14%. In our study also it was found to be more common in male i.e.76%.

Average age of onset has been described at 14-15 years and over 40 is rare (Lyons 1937)[5]. In our study 87.88% cases were found to be between 6-20 years of age.

Incidence is seasonal character 55% cases are reported to occur in summer (Neuman 1959)[6]. Its incidence has also been stressed to be five times greater in summer than winter (Papamatheacis 1962)[7] In our study maximum patients i.e. 42% cases were seen in the summer in the summer months and all cases bilateral.

The main clinical symptoms present in our study were itching, watering, redness, ropy discharge and photophobia. All these symptoms are typically seen in cases of vernal keratoconjunctivitis. 100% improvement seen in all symptoms after treatment.

The main clinical signs evaluated in our study were conjuctival hyperemia (100% cases), gelatinous ring around limbus (88% cases), papillary hypertrophy (82% cases) mucoid nodules around limbus (50% cases), cobblestone lesions on superior tarsus in (18% cases) and corneal involvement (8% cases). All clinical sign are resolved after end of the therapy.

At the start of the study the drug was given twice daily. After improvement in sign and symptoms the frequency was reduced to once daily and thereafter to every alternate day.

Vichanond *et al* [8] used tacrolimus eye ointment 0.1% (ophthalmic preparation prepared by mixing oral tacrolimus capsules with ophthalmic base containing 80% paraffin, 10% liquid paraffin and 10% lanolin) in 10 patients with recalcitrant vernal keratoconjunctivitis. All patients responded rapidly to the treatment. The only adverse effect observed was transient stinging.

In our study we observed that both concentration (0.03% and 0.1%) are effective as therapy for recalcitrant vernal keratoconjunctivitis.

So we can conclude that sirolimus is an effective and safe drug and it can be used effectively in not only refractive vernal keratoconjunctivitis patients but also as a first line of therapy as no untoward side effects are observed even after long term use.

5. Conclusion

Sirolimus eye drop is effective and sare therepy for recalcitrant cases of vernal keratoconjunctivitis. Both concentrations of sirolimus are effective and safe but 0.1% has faster action than 0.03%. Higher concentration (0.1%) used in severe cases for 30 days followed by lower concentration (0.03%). Sirolimus eye drop is alternate of steroid drop for long term use.

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