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EFFICACY OF TACROLIMUS IN SUBEPITHELIAL INFILTRATE SECONDARY TO ADENOVIRAL KERATOCONJUNCTIVITIS.

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ABSTRACT

Purpose: The aim of this study was to work out the efficacy and safety of tacrolimus (0.03%) ointment for the treatment of subepithelial corneal infiltrates (SEIs) secondary to adenoviral keratoconjunctivitis.

Methods: This study is about patients of post adenoviral sub epithelial infiltrate who were treated with tacrolimus 0.03% eye ointment twice daily. We are assed the length of treatment, best corrected visual acuity before and after treatment, IOP changes, symptom score and SEI before and after treatment.

Results: Sixty-two eyes of Thirty-eight patients were included. Of them twenty-four (63.1%) had bilateral involvement. All of them were treated with 0.03% tacrolimus eye ointment. The average length of treatment was 117 days, and the mean follow-up duration was 183 days. After 4 months continuous treatment patients were improved (p<0.001%) in term of visual acuity, improved symptomatic score and reduced SEI score. No significant adverse effect noted except mild burning sensation in five (13.1%) patients.

Conclusions: Topical tacrolimus ointment is an effective option for treatment of subepithelial infiltrate associated with adenoviral keratoconjunctivitis.

KEYWORDS : Adenoviral keratoconjunctivitis, subepithelial infiltrate, tacrolimus,

INTRODUCTION

Adenoviral conjunctivitis is very common ocular infection which may sometime causes an epidemic. In India it is mostly caused by Human adenovirus 8 (HadV-8) as well HadV-37, HadV-4, HadV-3 (1. 2). Normally infection transmitted via tear fluid or fomites. Normal incubation period ranges from 2-14 days (3). Patients first appears with the features of conjunctivitis but multifocal subepithelial corneal infiltrate (SEI) appears on undersurface of corneal epithelium after few days (4). These develop due to cellular immune reaction against viral antigen that are deposited in the superficial corneal stroma underneath the bowman membrane (5). There is disruption of collagen fibre in bowman layer with infiltration of lymphocytes, histocytes and fibroblast (6). These infiltrates often associated with photophobia, glare, foreign body sensation even reduced visual acuity (7). Sometimes these infiltrates persist several months even years (8). As it is due to immunogenic reaction dexamethasone e ye drop tries previously to resolve it but raised IOP is a major limitation (9). Then cyclosporine tried to resolve this with limited success (10).

Tacrolimus, a more potent immunosuppressant act by inhibiting the enzyme calcineurin and thus inhibits T cell activation (11).

The present study we evaluate the efficacy and safety of tacrolimus in patients with multifocal subepithelial infiltrate seen after adenoviral keratoconjunctivitis.

METHODS

It was a prospective nonrandomized non-comparative interventional study conducted over a period of one year from Jan 2019 to January 2020. During this period 47 patients attend our clinic with clinical presentation of multifocal subepithelial infiltrate in one or both eyes. All of them had the history of adenoviral conjunctivitis at least 30 days back.

All patients were clinically examined by slit lamp biomicroscopy for number and depth of infiltration. Intra-ocular pressure was measured by non-contact tonometry (CT 80, Topcon, Japan). Best corrected Visual acuity was recorded in LogMAR unit. Subepithelial infiltrate graded from 0-3 on slit lamp biomicroscopic examination. Here 0; no infiltrate, 1; mild infiltration, 2; moderate and 3; severe infiltration. Similarly, symptom score also graded from 0-4. Zero for no symptom and then 1 added to the to every symptom a) reduced vision b) burning sensation c) foreign body sensation d) redness.

Inclusion criteria

I. Confirmed case of adenoviral conjunctivitis at least one month back.
ii. Intra-ocular pressure 21 mm Hg or below.
iii. Age above 18 years.

After getting written informed consent from all eligible patient were advised to apply tacrolimus eye ointment (0.03%) twice daily in the affected eye. In all patient we demonstrate how to apply it to reduce over or faulty application related side effects. All patients were followed up at monthly interval. At each visit we record best corrected visual acuity, symptom score, SEI score and IOP. The final data recorded at 4 months and analyzed statically by pair T test.

RESULT

During the study period 47 patients attend to our outpatient department with post adenoviral subepithelial infiltrates. Of them 38 patients (62 eyes) met the inclusion criteria. 24 patients (63.1%) of them had bilateral involvement. Twenty-three (60.5 %) were male and remaining fifteen (39.5%) were female. The mean age of the patients was 38±12 years.

The average duration of tacrolimus therapy was 118 days and mean follow up duration was 171 days. Average best corrected visual acuity was 0.60 logMAR unit. Mean symptom score was 3.9 while average subepithelial infiltrate score was 2.9.

The pre-treatment epidemiological and clinical feature described in table 1.

Table 1: Baseline characteristics of patients

Variable	Mean	Standard Deviation
Age	38 yrs.	12 yrs.
Visual acuity (LogMAR)	0.60	0.16
Symptom Score	3.9	2.1
SEI score	2.9	0.3
IOP	16.9 mm Hg	2.1 mm Hg
Duration of Treatment	117 days	9 days
Follow up Duration	183 days	13 days

After 4 months application of tacrolimus (0.03%) ointment patients' visual acuity, symptom score as well as SEI score improved (table 2). During that time best corrected visual acuity improved to 0.20 logMAR unit, while symptom score improved from a mean value of 3.9 to 0.8 which is statically significant (p<0.001). Sub epithelial score was also improved significantly (p<0.001), as its score improved from a mean value of 2.9 to 0.3. At 4 months change of intra ocular pressure was statistically nonsignificant (p=0.579).

Table 2: Outcome measures at 4 months

Variables	At Baseline	At 4 months	p-value
Visual acuity	0.60±0.16	0.20± 0.13	<0.001

Symptom score	3.9±2.1	0.8±1.4	<0.001
SEI score	2.9±0.3	0.3±0.2	<0.001
IOP	16.9±2.1 mm Hg	17.1±1.9 mm Hg	0.579

No notable adverse effect noted in any patient except mild burning sensation in 5 (13.1%) patient during initial period. Although all of the study participant continues treatment protocol throughout the study period.

DISCUSSION

Corneal subepithelial infiltrate following adenoviral keratoconjunctivitis causing significant ocular morbidity. Till now there is no specific guideline regarding management of acute adenoviral conjunctivitis. Recently combined therapy of 0.6% povidone iodine with 0.1% dexamethasone show some success (12).

The use of topical steroid for subepithelial infiltrate is controversial. Butt, Chodosh et al. suggested use of topical steroid in patient with pseudomembrane and symptomatic subepithelial infiltrate but their finding was inconclusive regarding its preventive effect on the development of corneal SEI (13). Steroid are also associated with its well-known side effect like raised IOP & Cataract formation.

Then cyclosporine used by different researcher at various concentration. It showed some level of success but it also prolonged the duration of viral shedding and thus increase the chance of epidemic outbreak.

In this clinical study we measure the effectiveness and safety of 0.03% tacrolimus in post adenoviral keratoconjunctivitis subepithelial infiltrates.

Our results are encouraging. There was statically significant improvement of vision as well as reduction of subepithelial infiltrate & symptom scores after 4 months ($p<0.001\%$). Levinger et al. also reported a significant improvement of visual function in patients treated with 0.03% tacrolimus ointment after 18 weeks (14).

There was no significant rise of intra-ocular pressure seen in any patient after continued use of tacrolimus for 16 weeks. Only 5 patients reported mild burning sensation during initial period of tacrolimus therapy. Although within two weeks, this burning sensation ceased and all the 5 patients continue treatment protocol.

One of the biggest problems of SEI management is recurrence after cessation of therapy. Prado et al. observed a recurrence rate of 18.8% in tacrolimus therapy (15). Another recent study in India had recurrence rate of 7.5% after 6-month application of tacrolimus (9). We are treated the study population with 4-month application of tacrolimus twice daily and to prevent recurrence we continued it once daily for another 2 months. At 6 months our recurrence rate was 6.1%.

CONCLUSION

Topical tacrolimus 0.03% ointment is a good therapeutic option for treating post adenoviral subepithelial infiltrate with minimal adverse effect with low recurrence rate. Although we have a small single centre study, hence a large multicenter trial with longer duration will be beneficial in these regards.

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