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Original Research Article

A study on the use of topical bepotastine besilate ophthalmic solution (BBOS) 1.5% in the treatment of allergic conjunctivitis

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Abstract

The study was conducted to ascertain the efficacy and safety of topical bepotastine besilate solution (BBOS) 1.5% in controlling allergic conjunctivitis. The study design was randomized and out-patient department (OPD) based. Total 50 patients were included. They had symptoms and signs of allergic conjunctivitis. Symptoms included ocular itching, conjunctival redness, watering running nose, lacrimation, photophobia and foreign body sensation and signs included papillae, follicles, chemosis, hyperaemia and cobblestones. The data was gathered together after detailed history taking. We recorded baseline symptoms score(BSS) of each patient who fulfilled the inclusion and exclusion criteria. After that we started topical BBOS 1.5% one drop twice daily for 21 days and advised patients to immediately stop the drug and review in OPD in case of any aggravation of symptoms or burning sensation.

We examined patients on each follow up day 7, day 14 and day 21 by slit lamp biomicroscopy and recorded total mean symptoms and signs. Symptoms of allergic conjunctivitis especially ocular itching subsided within 7 days of the treatment, while other significant signs and symptoms subsided within 14 days of treatment. The interesting fact was observed that on 21st day of follow up cobblestones were flattened.

To conclude the use of bepotastin besilate 1.5% topically leads to an improvement in sign and symptoms in a significant number of patients. No significant side effects were noticed and patient compliance has been encouraging.

We recommended the use of BBOS 1.5% eye drop in all patents of mild to moderate allergic conjunctivitis.

Introduction

Allergic conjuctivitis(AC) is one of the most common allergic ocular eye disease. The hallmark feature of AC is ocular itching and conjunctival redness(hyperaemia). It is often accompained with lacrimation, photophobia, chemosis, lid swelling, running nose and foreign body sensation. There are 2 phases of allergic reactions. Acute phase occur within few seconds to minutes of allergen exposure like dust, pollen, molds, etc. It is an acute conjunctival reaction to the environmental allergen, most commonly pollen. It is an immediate type 1 hypersensitive reaction mediated by IgE and subsequent mast cell activation, subsequently mast cells de granulate in response to the action of IgE.

AC is two types seasonal AC (SAC) and perennial AC (PAC).

The onset of symptoms of SAC is seasonally related to circulatory aero antigen specially pollens. It may be associated with hay fever (allergic rhinitis) and also be known as hay fever conjunctivitis.

PAC is the variant of SAC that persists throughout the year. It is a response to perennial allergens such as house dusts, mites etc. It is chronic in nature and occurring throughout the year. In acute case Clinical symptoms and signs are typically bilateral and consist of itching, burning, and mild to moderate injection that can progress to various degrees of glassy chemosis. A watery or mucoid discharge may be seen.

The late phase(chronic) generally occur hours or day after exposure of allergens and manifested by pro inflammatory mediators like Leukotrine B4 (LTB4) and immune cells like eosinophils and neutrophils.Clinical symptoms include intense ocular itching, burning, tearing,photophobia, and a stringy mucus discharge. Periorbital eczema, lid edema, and conjunctival chemosis are common finding. On the superior tarsal conjunctiva cobblestone papillae may occur. Gelatinous limbal hyperplasia and nodules may be present with or without Horner–Trantas dots (areas of eosinophils and degenerating cellular debris). In severe cases, cicatrizing conjunctivitis with subepithelial fibrosis, symblepharon formation, and forniceal shortening may develop.

The allergic reactions may limited to eye or it may be the part of generaized allergic reaction with nasal and respiratory symptoms.Clinical signs and symptoms are typically bilateral and predominantly cause by the action of

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histamines which is derived from mast cells. Allergic conjunctivitis clinically diagnosed by both patients' symptoms and signs. AC treatment includes avoidance of offending agent, topical mast cell stabilizer, antihistamines, artificial tear drops like carboxy methyl cellulose, cold compression and corticosteroids.

Mast cell stabilisers like sodium chrymoglycate are very effective in preventing recurrence in atopic cases. Artificial tears provide soothing effect. Dual action antihistamine and mast cells stablizers like olopatadine, bepotastin besilate, azelastine effective for exacerbation. Corticosteroids are reserve for severe to resistant cases of AC.

Histamines released by mast cells acts on H1 (histamine1) and H2 (histamine 2) receptors in the surrounding ocular tissues and causes immunomodulatory effects, itching, swelling, erythema, pain and increase vascular permeability. These side effects are mainly due to action of histamine on H1 receptor. So the first line therapy of AC includes drugs which stablizes mast cells and diminishes its degranulation and those which directly antagonise the action of histamines.

Bepotastine besilate is a piperidine derivative with dual action agent and a highly selective antihistamine(H1 receptor blocker). It is also a potent mast cell stabilizer. It also inhibit leucotriene B4 and attenuate eosinophil chemotaxis and activation so acts as an anti-inflammatory agent too. It may also inhibit interleukin 5 platelet activating factor. Thus bepotastine besilate is a medication with a number of mechanisms of action.

Many studies revealed that it has limited blood brain barrier penetration. Plasma concentrations peaks 1-2 hours after instillation of eye drop.

Many positive studies have been done in Japan in which oral preparation of bepotastine besilate was approved by Japanese ministry of health and welfare in July 2000 for the allergic rhinitis treatment and then in 2002 for the treatment of urticaria and pruritis of skin. In the year 2009, the BBOS was also approved by the agency called Food and Drug Administration (FDA) for allergic conjunctivitis. After getting the approval in Japan the medicine bepotastine was reformulated on the basis of its clinical effectiveness in the gradually collected results for its topical use in the treatment of AC.

Other studies have also been done to study the attributes like the efficacy, safety and comfort of the medicine in the treatment of AC. To measure the efficacy and safety of ophthalmic anti allergics, these clinical trials used the conjunctival allergen challenge (CAC) model. The CAC model based clinical trials (one single site and one multisite) showed that bepotastine besilate opthalmic solution (BBOS) (either 1.0% or 1.5%) gave a clinically significant reduction in ocular itching for up to 8 hours after instillation of drugs. Along with this, it also causes statistically significant reductions in conjunctival redness associated with AC. Thus, these studies established the clinical safety and effectiveness of BBOS 1.5% and its specific approval for the treatment of ocular itching associated with AC.

Materials and Methods

The study was conducted in department of ophthalmology, PMCH with study design of randomized OPD basis included 50 patients of AC with mean age 25yrs with presenting complains of itching, rednes, lid swelling, watering, photophobia, running nose and foreign body sensation. At first written informed consent (or parental/guardian permission in patients less than 18 years of age) was taken from all patients before any clinical study procedures were conducted. In this present study perennial allergic conjunctivitis (PAC) was taken under consideration.

Inclusion Criteria

All the patients (Male or Female) greater than 9 years of age who:

1. Were willing to attend all study visits
2. Had good compliance for the given drugs.

Exclusion Criteria

Subjects i.e. the patients (M/F) were excluded in the study if:

1. They were not willing to attend all the visits made for the study.
2. The subject who had not gone under medication for
   a. Active ocular diseases.
   b. Clinically significant diseases like meibomianitis, blepharitis, keratitis, uveitis
   c. Severe cardiovascular diseases
   d. Significant illness (like angle closure glaucoma)

As this could affect the study results.

3. Had a known contraindications to the use of any study drugs or their components.

After considering inclusion and exclusion criteria, a detailed history was recorded including history of allergy, use of topical steroid or antihistamines, bronchial asthma, allergic rhinitis and significant family history.

On first visit visual acuity, slit lamp bio microscopy was performed and baseline ocular symptoms were recorded which included itching, redness, lid swelling, watering, running nose, discharge, photophobia and foreign body sensation. Each symptom was scored on a 0 to 4 point scale (0=no symptom, 4=very severe) The sum of all these symptoms were total symptom score(TSS). Baseline TSS were recorded before starting medication.

Similarly signs were recorded included pappila, chemosis, follicles, cobblestones. Patients were treated with Bepotastine besilate 1.5% eye drop with dosing one drop twice daily (7am-7pm) and then followed upon day 7,14,21 and thereafter fortnightly at intervals for 12 weeks. Patients were advised in any case of burning sensation or redness or any aggregations of symptoms occur then immediately stop the drug and visit in OPD. They were also advised discard the drug if it becomes cloudy or colour changes. We

instructed them at the time of administration of drug not to touch vial tip and avoid direct contact with eye. At each follow up visit, the compliance of treatment were asked. Then we did slit-lamp biomicroscopy and scored for symptoms and signs.

Results

The result depicted that out of 50 patients there were 28 males and 22 females with a mean age of 25 years. The primary usefulness of treatment was the overall decline in baseline in total symptom score (TSS) over period of 21 days.

Table 1: TSS Score

Average	Day 1	Day 7	Day 21
Symptoms	8.4	4.6	1.8
Signs	5.5	4.7	1.9

Responders were defined as patients whose TSS scores reduced by a minimum of 3 points from there baseline scores after 7 days of treatment.

Marked reduction of ocular itching and lacrimation was seen at the end of 7th day. Majority of the Patients reported that even after 5 minutes of instillation of topical BBOS 1.5% there intense ocular itching substantially relieved. Signs like follicles (yellowish white, round elevations, 1-2mm in diameter, occur due to localized aggregations of lymphocytes in the sub epithelial adenoids layer), papillae (hyperplasia of the normal vascular system with glomerulus-like bunches of capillaries growing into the epithelium in inflammatory conditions), chemosis (oedema of conjunctiva occurs due to exudation from the abnormally permeable capillaries) of conjunctiva regress at the end of 14th day. Cobblestone (Giant papillae assume a flattop appearance, present on the superior tarsal of conjunctiva) flattened at the end of 21st day.

In order to determine the extent to which subjects i.e. the patients can experience complete relief from ocular itching when exposed to allergens, we examined the percentage of subjects with "itch scores" of zero at each time point following BBOS 1.5%. The result obtained was over one-half (i.e. around 55%–68%) of the subjects reported they got completely relief (no itch) within 5 minutes of instillation of BBOS 1.5%.

Adverse Effects

Bepotastin besilate does not have significant activity against H3, adrenergic, muscarinic, and benzodiazepine receptors so does not have the undesirable side effects of other antihistamines. Also many animal studies conclude that bepotastin has no side effect on the respiratory and circulatory system with usual doses.

Out of 50 only 5 patients reported a mild altered taste after instillation of drug. During study period none of the patients were discontinued from the treatment. No other significant adverse effects were reported.

Discussion

The prevalence of allergic conjunctivitis disease and its side effects on vision and ocular comfort increases day by day so necessity the use of safe, highly effective, and comfortable topical drugs for its treatment.

When topical BBOS 1.5% given to the patients of AC it effectively relieve even an intense ocular itching within 7 days of treatment. Although patients reported that even within 5 min of instillation of medication itching started relieving.

In the year 2009, September, the US Food and Drug Administration (FDA) approved the BBOS 1.5% for the treatment of itching associated with AC on the basis of results of CAC based trials of BBOS 1.5%.

Oral bepotastine is presently not approved in the United States. It is used in Japan for the treatment of urticarial, allergic rhinitis, allergic conjunctivitis and allergic pruritis related to skin diseases. BBOS is an antiallergic agent with dual action of a potent mast cell stabiliser and a highly selective H1 receptor antagonist. This study showed that the majority of cases of AC can be effectively and safely treated with topical BBOS 1.5%.

In one study it was also proved that BBOS is 66.7% more superior in relieving ocular itching specially evening ocular itching than olopatadine. Although olopatadine is also an antihistamine with dual action of selective H1 receptor antagonist and mast cells stablizer like BBOS. Many trials revealed that bepotastine is an effective, useful and well tolerated antihistamine drug in the treatment of urticarial, allergic rhinitis, allergic conjunctivitis and allergic pruritis related to skin diseases.

Conclusion

From the above study done, we concluded that BBOS 1.5% is a clinically proven very safe and highly effective eye drop with no any significant adverse reaction. Most importantly, it provides a rapid and sustained reduction in ocular itching, even for the most severe AC sufferers and also a significant relief for other allergy associated symptoms and signs.

We recommended the use of BBOS 1.5% eye drop in all patients of mild to moderate disease of AC.

This study states the usefulness of BBOS 1.5% for treating AC in a more considerable sized sample of allergy subjects. It concluded that BBOS 1.5% is an effective anti-allergic drug that provides rapid and sustained reduction of ocular itching, even for the most severe AC sufferers. It also shows that it provides remarkable relief for other allergy associated symptoms and signs of eye. It is a safe and highly effective anti-allergic medication having no noteworthy adverse effects.

We recommended the use of BBOS eye drop in all patients of mild to moderate disease of AC.

Disclosure

Authors do not have any financial conflicts of interest in any material or method mentioned in this study.

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Conflict of Interest: None.

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