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Original Article

Safety and Efficacy of the combination of Naphazoline Hydrochloride, Hydroxy Propyl Methyl Cellulose, Boric acid, Borax, Menthol and Camphor in patients of Ocular allergy and Ocular inflammation of a non-infectious origin

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ABSTRACT

Objective: Ocular allergy is an inflammatory response by an allergen when it interacts with IgE bound mast cells. Ocular redness, ocular itching and ocular discharge are the main symptoms. Naphazoline is ocular decongestant used for the treatment of ocular redness. Hydroxy Propyl Methyl Cellulose (HPMC) moistens, soothes and lubricates the ocular surface. Boric acid and Borax are Anti-inflammatory/mild Anti-infective while Menthol and Camphor are used to give soothing effect to the eye.
Methods: Of 216 patients, 205 patients completed the study. 11 patients were lost to follow-up. Efficacy assessment was done by studying the reduction in Visual Analogue Scale (VAS) of ocular redness, itching and discharge at day 3 and day 5 as compared to baseline. Safety assessment was made by analysing the adverse events during the clinical trial.
Results: Mean VAS score of ocular redness, ocular discharge and ocular itching was 4.71, 3.07 and 4.22 (baseline) at visit 1 respectively which was slightly reduced to 2.33, 1.45 and 2.12 (day 3)at visit 2 respectively and it was further reduced to 1.07, 0.83 and 0.65 (day 5) at visit 3respectively.
Conclusion: Combination of Naphazoline, HPMC, Boric acid, Borax, Menthol and Camphor is safe and effective in the treatment of Ocular allergy.

Keywords: Ocular allergy, Naphazoline Hydrochloride, Hydroxy Propyl Methyl Cellulose, Boric acid, Borax, Menthol, Camphor, Visual Analogue Scale (VAS).

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INTRODUCTION

Ocular allergy (OA) or Allergic conjunctivitis (AC)comprise a group of hypersensitivity disorders to normally harmless substances, known as allergens and are related with rhinitis, asthma, atopic dermatitis or food allergy[1]. The most common clinical appearance of OA are conjunctival hyperaemia (redness) and chemosis (swelling), itching and tearing and vision loss in many cases [2].A study conducted by the American College of Allergy, Asthma and Immunology found that 35% of families experienced allergies, of which more than 50% reported associated eye symptoms[3]. The significance of OA results mainly from its frequency, which ranges from 5% to 22% of the population [4].

OA is a comprehensive term that encompasses seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC). However, VKC and AKC have clinical and pathophysiological features are quite different from SAC and PAC, in spite of some common markers of allergy [5]. Also contact lenses or ocular prosthesis related giant papillary conjunctivitis (GPC) are often included in the group of ocular allergy, however they should not be considered as real allergic diseases, but as chronic ocular micro-trauma related disorders, which need to be managed by ophthalmologists in association with contact lenses experts[6].

OA is an inflammatory response caused by an allergen when allergens interact with IgE bound sensitized mast cells and thus activation of mast cells causes enhancement of tear levels of tryptase, histamine, leukotriene and prostaglandins. Therefore, results into ocular allergy or allergy conjunctivitis. Mast cells activation is chief to the pathophysiology of SAC, PAC, VKC, AKC and GPC [7, 8]. However the instant onset of ocular itching is directly the result of mast cell-released histamine, the release of companion proinflammatory mediators attracts neutrophils, T cells, basophils, and eosinophils, which all intensify later stages of the allergic response [7, 9].

While mast cells enduringly reside in conjunctival tissues, basophils circulate in the blood and migrate to sites of inflammation when called in by locally released chemokines. Basophils also express the IgE receptor; they release histamine along with other mediators, and play an important role in the development and maintenance of allergic inflammation. Increased concentrations of T cells may be present in SAC and PAC, while mast cells seem capable of instigating IgE production independently of T cells[7, 10]. T cells are the major players in all more severe allergic diseases.

Therefore for the treatment of ocular allergy and ocular inflammation of a non-infectious origin, combination of Naphazoline Hydrochloride, Hydroxy Propyl Methyl Cellulose (HPMC), Boric acid, Borax, Menthol and Camphor can be used in the FDC. Naphazoline Hydrochloride are vasoconstrictors which are used for the treatment of ocular redness or ocular vasodilation, HPMC moistens, soothes and lubricates the ocular surface. While Boric acid + Borax are Anti-Inflammatory and mild Anti-Infective against fungus and bacteria, Menthol and Camphor gives cooling and soothing effect to the eyes. So all these drugs can be used in theOculardosage form for treatingthe symptoms of ocular discharge, ocular itching and ocular redness as well as to reduce the ocular inflammation.

0.1% w/v Naphazoline hydrochloride can be used as ocular decongestant. It acts on alpha 2 adrenergic receptor agonist thus it will constricts the vascular system of the conjunctiva and resulting in decreased in conjunctival congestion [11, 12]. It has an advantage of long lasting relief from redness upto 8 hours [13].

Boric acid and Borax has a mild Anti-infective properties which is active against fungal and bacterial infection. It provides soothing relief from eye irritation, and helps remove pollutants from the eye. Along with Anti-infective it has Anti-inflammatory properties thus reduces inflammation and pain[14].

Hydroxy Propyl Methyl Cellulose (HPMC) moistens, soothes and lubricate the ocular surface, thus it will relieve the eye dryness and soreness[15].Low concentration of Menthol (0.0025% w/v) gives rapid cooling and soothing effect and Camphor at low concentration (0.0025% w/v) gives soothing and analgesic action.

METHODS

The Phase IV clinical study (PMS study) was conducted for the combination of Naphazoline hydrochloride, Hydroxy Propyl Methyl Cellulose (HPMC), Boric acid, Borax, Menthol and Camphor in patients of ocular allergy and ocular inflammation of a non-infectious origin at 14 centres in various cities of India. Only Registered Ophthalmologists were selected as an investigator for this phase IV clinical study. Study was conducted from January 2017 to April 2017. A total of 216 patients were recruited for the study, out of which 205 patients completed the study, 11 patients were lost to follow up during the study.

Inclusion and Exclusion criteria: This study included patients having age between 18 to 75 years of both the sex. Patients with eye allergy, eye inflammation, redness, discharge and itching were included in the study. Only the patients who are ready to strictly adhere to the protocol were recruited for the study.

Patients with hypersensitivity to the individual study drugs, high BP and known ocular hypertension were excluded. Pregnant or lactating women and Patients who cannot adhere to the protocol (mentally ill and patients with psychological problems) were excluded.

Sample size calculation: This study was conducted on 14 ophthalmology centres and at each centre each investigator was instructed do it on minimum 10 patients or maximum 16 patients. So the decided minimum number of patients were 120 but then the actual study was conducted on 205 patients.

Study Intervention: Study dosage- Combination of Naphazoline hydrochloride (0.1% w/v), Hydroxy Propyl Methyl Cellulose (0.2% w/v), Boric acid (1.0% w/v), Borax (0.05% w/v), Menthol (0.0025% w/v) and Camphor (0.0025% w/v) per ml.
Study dosage and administration – patients were asked to instil one to two drops of Ocurest Plus New Eye Drops four times a day for a study period of 5 days.

Study Protocol: The study duration was kept 5 days. Patients of ocular allergy and ocular inflammation satisfying the inclusion and exclusion criteria were recruited for the study. A detailed medical history was taken and physical examination (including the vital signs, systemic and general examination) was conducted and recorded by the investigators. Patients were dispensed with physician sample pack of study drug combination for ophthalmic use. Patients were asked to maintain a diary of all the symptoms and note any adverse event occurring in the study duration. Three visits were planned for the patients recruited in this study- V1 (baseline visit) on day 1, V2 (evaluation visit) on day 3 and V3 (conclusion visit) on day 5. VAS and adverse events occurring were noted on CRF during each visit along with medical history and physical examination by the investigator. Investigators were asked to discontinue the study drug in case of severe adverse event and with discretion, clinical experience in case of mild to moderate adverse events.

Concomitant therapy: No Pharmacological intervention and medication including oral or ocular anti-inflammatory or antibiotic drugs were allowed during the study period of 5 days.

Efficacy assessment: The primary assessment was reduction in VAS of ocular itching, ocular redness and ocular discharge on an eleven point scale (0 to 10) where 0 is no symptoms and 10 is maximum tolerated symptoms. The secondary assessment was number of patients having no symptoms (0 on VAS) on day 5 and number of patients having more than 50% reduction in VAS.

Safety assessment: Patients were asked for any adverse event and the same if present was noted in the case record form during each post-dose visit. These adverse events were classified into serious adverse events and non-serious adverse events. Naranjo's scale of probability was used to classify the adverse event as drug related or nondrug related. Adverse events were followed up by the investigators till their resolution.

Regulatory matters: The study drug combination is approved for manufacturing and marketing in India. The FDC Naphazoline hydrochloride (0.1% w/v), Hydroxy Propyl Methyl Cellulose (0.2% w/v), Boric acid (1.0% w/v), Borax (0.05% w/v), Menthol (0.0025% w/v) and Camphor (0.0025% w/v) per ml is available under various brands in India andclassified under schedule H drugs i.e. it can be sold only in the presence of a prescription of a registered medical practitioner only. All the patients recruited in the study have read informed consent form and signed the same. Clinical trial protocol, ICF, CRF, undertaking by the investigators form, ethical committee certificates were collected before initiating the clinical study.

RESULTS

A total of 216 patients were recruited at 14 centers across India, 205 patients completed the study and were analysed.Mean VAS score of Ocular Redness, Ocular Discharge and Ocular Itching at each visit was evaluated and individually plotted graphically as shown in figure 1. The percent reduction in mean VAS score in Ocular Redness, Ocular Discharge and Ocular Itching at visit 2 and 3 was evaluated and plotted in figure 2. At baseline the mean VAS score for Ocular Redness, Ocular Discharge and Ocular Itching was 4.71, 3.07 and 4.22 respectively. On visit 2 i.e. day 3 the mean VAS score for Ocular Redness, Ocular Discharge and Ocular Itching was reduced to 2.33, 1.45 and 2.12 respectively. At visit 2 i.e. day 3 the percent reduction in mean VAS score for Ocular Redness, Ocular Discharge and Ocular Itching was found to be 50.53%, 52.76% and 49.76%. On visit 3 i.e. day 5 the mean VAS score for Ocular Redness, Ocular Discharge and Ocular Itching was further reduced

to 1.07, 0.83 and 0.65 respectively. Similarly at visit 3 i.e. day 5 the percent reduction of Ocular Redness, Ocular Discharge and Ocular Itching was found to be 77.28%, 72.96% and 84.59% in mean VAS score.

DISCUSSION

The clinical trial conducted to study the safetyand efficacy of a FDC of Naphazoline hydrochloride, Hydroxy Propyl Methyl Cellulose, Boric acid, Borax, Menthol and Camphor in reducing the symptoms of Ocular redness, Ocular itching and Ocular discharge.

Strong point of this clinical trial is that Visual Analog Scale (VAS) is used as a criterion for efficacy calculation. VAS is used for analysing the main and common symptoms of Ocular redness, Ocular itching and Ocular discharge at all the visit so that we could identify the safety and efficacy of the drug.

At baseline (V1) the mean VAS score for Ocular Redness, Ocular Discharge and Ocular Itching was 4.71, 3.07 and 4.22 respectively. On visit 2 i.e. day 3 after giving medication the mean VAS score for Ocular Redness, Ocular Discharge and Ocular Itching was reduced to 2.33, 1.45 and 2.12 respectively. At visit 2 i.e. day 3 the percent reduction in mean VAS score for Ocular Redness, Ocular Discharge and Ocular Itching was found to be 50.53%, 52.76% and 49.76%. On visit 3 i.e. day 5 (last visit) the mean VAS score for Ocular Redness, Ocular Discharge and Ocular Itching was further reduced to 1.07, 0.83 and 0.65 respectively. Similarly at visit 3 i.e. day 5 the percent reduction of Ocular Redness, Ocular Discharge and Ocular Itching was found to be 77.28%, 72.96% and 84.59% in mean VAS score. Therefore, the study drug medication was found to be safe and effective in treating Ocular redness, Ocular itching and Ocular discharge.

Mark B *et al* conducted a study to compare the effects of eight ocular decongestant eye drops in red eye. The eight ocular decongestants eye drops includes 0.1% Naphazoline hydrochloride, 0.01% Naphazoline hydrochloride, 0.05% Naphazoline hydrochloride, 0.02% Naphazoline hydrochloride, 0.012% Naphazoline hydrochloride, combination of 0.012% Naphazoline hydrochloride and 0.1% antipyrine, 0.05% Tetrahydrozoline hydrochloride and the combination of 0.12% Phenylephrine hydrochloride and 0.1% antipyrine were used to compare their efficacy with each other. The study was conducted on six human subjects in seven sessions. All ocular decongestant were effective. In fact, concentration of Naphazoline 0.02% was found to be more effective than other ocular decongestant[16].

Mark B *et al* evaluated a clinical trial on two ophthalmic vasoconstrictors to check its whitening ability, duration of action, tolerance and rebound vasodilation in 11 normal volunteers. 0.02% Naphazoline HCL and 0.05% Tetrahydrozoline HCl significantly reduced redness after a single use. But Naphazoline produced significantly more whitening than Tetrahydrozoline and also retained its whitening ability after ten days. The level of redness remained significantly below baseline for eight hours after a single use of either vasoconstrictor and for six hours after multiple use of Naphazoline[17].

CONCLUSION

The combination of Naphazoline hydrochloride (0.1% w/v), Hydroxy Propyl Methyl Cellulose (0.2% w/v), Boric acid (1.0% w/v), Borax (0.05% w/v), Menthol (0.0025% w/v) and Camphor (0.0025% w/v) was found to be effective and safe in treatment of ocular allergy and inflammation.

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DISCLOSURE

This study was conducted as a part of Pharmacovigilance activity for Ocurest Plus New Eye Drops manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd. in accordance with Pharmacovigilance Program of India (PvPI).

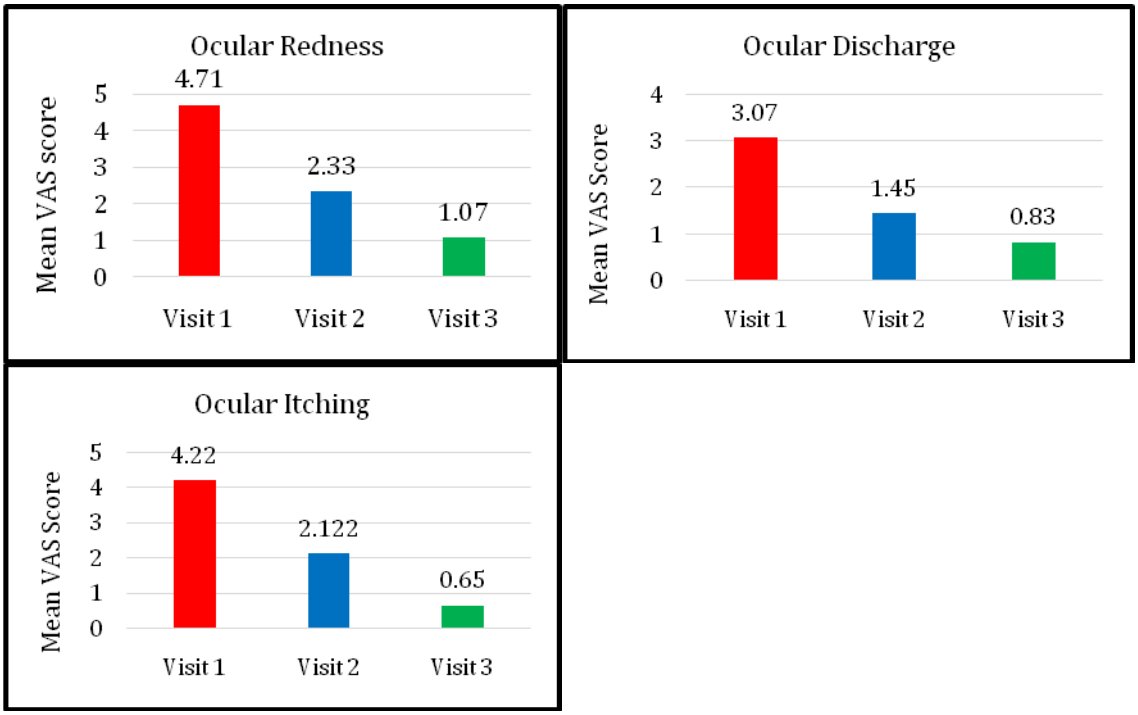

Figure 1: Reduction in mean VAS score in Ocular Redness, Ocular Discharge and Ocular Itching at each visit.

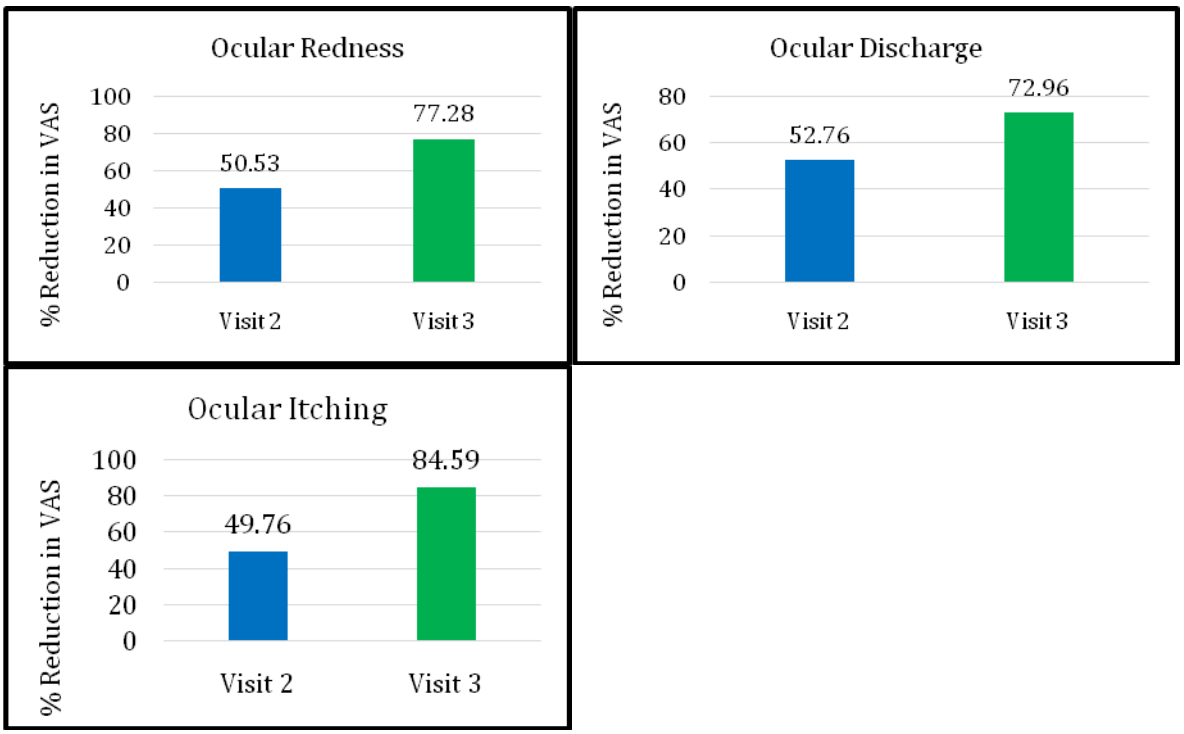

Figure 2: Percent reduction in mean VAS score in Ocular Redness, Ocular Discharge and Ocular Itching at each visit.

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