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SAFETY AND EFFICACY OF A TOPICAL COMBINATION OF PHENYLEPHRINE AND NAPHAZOLINE FOR MANAGEMENT OF OCULAR REDNESS: PHASE IV CLINICAL STUDY

Dr. Mayuresh Kiran*[1], Sharvari Lotankar[2] and Lalit Pawaskar[3]

[1]Vice-President, Medical Services, Centaur Pharmaceuticals Pvt. Ltd.
[2]Officer, Medical Services, Centaur Pharmaceuticals Pvt. Ltd.
[3]Research Associate, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd.

***Corresponding Author: Dr. Mayuresh Kiran**

Vice-President, Medical Services, Centaur Pharmaceuticals Pvt. Ltd.

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ABSTRACT

Introduction- Red eye is the cardinal sign of ocular inflammation and one of the most common ophthalmologic conditions in the primary care setting. Inflammation of almost any part of the eye, including the lacrimal glands and eyelids, or faulty tear film can lead to red eye. Primary care physicians often effectively manage red eye, although knowing when to refer patients to an ophthalmologist is crucial. A combination of Phenylephrine which is selective, potent, alpha 1 adrenergic receptor agonist has capillary decongestant action in the eye and Naphazoline which is an imidazoline derivative, is an alpha (2)-adrenergic agonist, gives vasoconstrictive and decongestive properties in the eye. This Phase IV study trial evaluates the efficacy and safety of the combination of Phenylephrine and Naphazoline for the treatment of Allergic Rhinitis or Allergic Asthma. **Methodology** -Total 140 patients were recruited for the study, of which 124 patients completed the study trial and 16 patients were lost to follow up. Assessment of the efficacy was made by the reduction in TSS and four point Likert-type scales. Safety assessment was done by analyzing the adverse events during the trial. **Results-** The reduction in TSS from 4.2 (baseline) to 2.008 (day 3) and 0.702 (day 5) was observed. 12 episodes of adverse events occurred and reported which were of mild intensity. **Conclusion-** A combination of Phenylephrine and Naphazoline is safe and effective in the treatment of Ocular Redness.

KEYWORDS: Phenylephrine, Naphazoline, Ocular Redness.

INTRODUCTION

Redness of the eye is a common ophthalmic symptom which forms a big proportion of the eye problems seen in most eye clinics in the developing countries.[1,2] A red eye usually mirrors the possible reactions of the eye to both exogenous or endogenous irritants and trauma, thus giving an indication of the possible ocular diseases.[3]

The causes of a red eye can be numerous and it can occur as an ophthalmic emergency within minutes or hours but also as a chronic disease over weeks or months. In general, redness of the eye is the cardinal sign of ocular inflammation that can be caused by hyperemia with dilation of the conjunctival, episcleral, or scleral vessels (trauma, chemical burns, immunologic reactions); inflammatory reactions from infections (bacterial, viral, fungal); leading to inflamed blood vessels in the eye or chronic reactions of the external eye from systemic causes (Sjörgen's syndrome).[3,4,5]

The condition of red eye is usually benign and can be managed primarily by the physicians. There are various factors causing the redness of the eye and the causes can be classified as painful red eye, trauma, and other common conditions. Conjunctivitis is reported to be the most common cause of the red eye condition. The causes to consider in patients with suspected acute conjunctivitis are allergic; bacterial (staphylococci, pneumococci, gonococci, haemophilus); viral (adenovirus, herpes viruses); and chlamydial. Apart from conjunctivitis other common causes of Red eye include dry eye, blepharitis, corneal abrasion, foreign body, subconjunctival hemorrhage, keratitis, iritis, primary acute closure glaucoma, chemical burn and scleritis or penetrating trauma.[1]

A careful history and simple examination along with the typical clinical signs are important for the management of this common disorder which is usually characterized by redness of the eye, eye discharge, pain, photophobia, itching along with the visual changes.[1] Red eye usually ranges from simple inflammation following itching along with minor trauma like severe cases like orbital cellulitis and tumors.[3] The red eye condition can be classified as

either sight-threatening or can be non-sight threatening as the patients presenting with painless red eye and normal vision usually recover well in time but red eye is associated with pain, photophobia, watering and blurring of vision, it appears to be potentially sight-threatening and need to be addressed urgently.

It is necessary to diagnose red eyes as early as possible based on the ocular symptoms encountered such as visual abnormalities, abnormalities in eye appearance, eye sensory abnormalities (pain), photophobia and ciliary flash. Red eyes are more common in men than women. Introducing dangerous causes of red eyes in the future can help to health care professional to on time diagnosis of red eyes related problems. Injury (or trauma) Traumatic injuries form about 10% of all red eyes. These injuries may cause irreversible damage to the eye leading to blindness. Many of these would need immediate referral to a secondary or tertiary eye care facility.

Phenylephrine hydrochloride is a potent, effective, relatively safe drug with few ocular side effects thus used for treatment of number of eye allergies and infections.[5] Phenylephrine is directly acting sympathomimetic amine and an alpha adrenergic receptor agonist which stimulates the with minimal or no β-receptor effect. Traditionally, the topical phenylephrine 10% is used by ophthalmologists for pupillary dilatation and capillary decongestion in the eye. The action of phenylephrine to cause constriction of blood vessels in the eye helps in relieving eye redness, dryness, burning and irritation sensation caused by wind, sun and the other irritants. Systemic side effects after absorption of phenylephrine ranges from transient hypertension, angina, cardiac arrhythmias and syncope to fatal hemodynamic changes, subarachnoid hemorrhage, pulmonary oedema, myocardial infarction, left ventricular failure and death. Thus, a concentration of 2.5% is used since it is safe.[6] Naphazolin which is an imidazoline derivative, is an alpha (2)-adrenergic agonist, is widely used as non-prescription eye preparation due to its vasoconstrictive and decongestive properties in the eye. This results in narrowing the swollen eye capillaries.[7] In conditions, Phenylephrine has fast onset of action Phenylephrine - fast onset of action i.e. clears the redness fast but has short duration (upto 6 hours) whereas Naphazolin has slow onset of action but the action lasts for long duration of (6-8 hours).Menthol, a member of the monoterpene class of phytochemicals are found in plant derived essential oils. Menthol is associated to have anti-oxidant, anti-inflammatory along with analgesic effects. The TRP i.e transient receptor potential channels demonstrate the cooling actions of menthol.[8] Camphor is a naturally occurring substance used as a soothing agent and also associated as a topical analgesic properties.[9] Benzalkonium chloride (BZK) formulations are frequently used as antiseptics in healthcare and consumer products.[10]

MATERIALS AND METHODS

A phase 1V, open-labeled, Multicentric, Post-Marketing Surveillance (PMS) trial was conducted across 12 centres across India for duration of 5 days. A total of 140 patients were screened for the study of which 124 patients completed the study and 16 patients were lost to followup. to substantiate the Safety and Efficacy of Ocurest Eye drops in patients of ocular congestion, redness and inflammation of a non-infectious origin.

Inclusion criteria: The present clinical study included both the male and female patients between the age group of 18-75 years. The enrolled patients were confirmed to be diagnosed with eye inflammation, redness, discharge and itching along with patients with high blood pressure and known ocular hypertension in the study. The patients that can adhere to this protocol were included in the study.

Exclusion criteria: This clinical study trial excluded patients that were thought to be hypersensitive to the study drugs. Pregnant and lactating mothers were barred from the study. Also patients diagnosed with Psychological problem and psychiatric illness and those who cannot give informed consent were excluded from the study trial.

Study intervention: Ocurest Eye Drops 7.5 ml free sample bottle was provided to the patients free of cost by the sponsor. Study dosage and administration- Patients were advised to instill one or two drops of Ocurest Eye Drops four times a day for a study period of 5 days.

Study Procedure: The clinical trial was conducted for a period of 5 days and all the eligible patients satisfying the inclusion and exclusion criteria were recruited for the study. All the eligible patients were informed of the nature of the study and an informed consent was obtained for the same. A detailed medical history was taken by thorough clinical examination and physical examination that included the vital signs, systemic and general examination was conducted by the investigators. Patients will be given Ocurest Eye Drops 7.5 ml free sample bottle and ask to instill one or two drops of Ocurest Eye Drops four times a day for a study period of 5 days. A diary of the daily symptoms has to be maintained by the patients. In cases when the patient encounters adverse events and safety-related issues, the investigator can withdraw the patient from the clinical trial and treat the patient as per the severity of the symptoms. Three visits were outlined for the patients recruited in this study- V0 (Baseline visit) day 1, V1 (reevaluation visit) day 5 and V2 (conclusion visit) day 10.Complete Medical history of the patient was recorded and physical examination along with the Total Symptom Score and adverse event occurring were esteemed during each visit. Investigators were asked to discontinue the study drug in case of serious adverse events and with discretion or clinical experience in case of mild to moderate adverse events.

Concomitant Therapy: No Pharmacological intervention and medication including topical decongestants (sprays, drops and aromatic oils), antibiotics, multi-vitamins and multiminerals were allowed during the study duration other than the study drug.

Non-pharmacological interventions like drinking warm/hot water at regular intervals and steam inhalation were allowed and encouraged during the study.

Efficacy Assessment

The primary assessment was done by analyzing the reduction in TSS (Total symptom score) which was a score of all the symptoms on a eleven-point scale (0 to 10) where 0 is no symptom and 10 means maximum tolerated symptoms. The TSS scale was further extrapolated to the Likert-type symptom severity scale with 4 grades- no symptoms (0 on TSS), mild (1-4 on TSS), Moderate (5-8) and Severe (9-10 on TSS).

Safety Assessment

Patients were questioned for any adverse event. All the serious and non-serious adverse events were fully documented using clinical charts, original documents and case report form. The adverse events were categorized into non-serious adverse events and serious adverse events. Naranjo's scale of probability was used to classify the adverse event as non –drug related or drug related. Adverse events were followed up by the investigators till the symptoms subside.

Regulatory and Ethical Matters

The said combination is available in India and is classified as the schedule H drug which means it should be sold only in presence of prescription of a registered medical practitioner. All the patients participating in the study have read and signed the ICF.

RESULTS

A Total of 140 patients were recruited at 12 centres across India. Out of which 124 patients completed the study and were analyzed.

Efficacy Analysis

Mean of the total symptom score (TSS) for Occular Redness was recorded at all the visits (V0, V1 and V2) and thus the reduction on TSS was calculated. The mean TSS at V0 or the baseline visit at day 1 was 4.2 which was reduced to 2.008 at V1 or day 3 and further reduced to 0.702 on V2 or day 5. Similarly, the Mean of the total symptom score (TSS) for Ocular discharge was recorded at all the visits (V0, V1 and V2) and thus the reduction on TSS was calculated. The mean TSS for ocular discharge at V0 or the baseline visit at day 1 was 2.42 which was reduced to 0.97 at V1 or day 3 and further reduced to 0.32 on V2 or day 5.Thus, there was a reduction in mean TSS score of 47.80% and 16.66% for ocular Redness.

The reduction of TSS every visit for ocular Redness and ocular itching has been shown in figure 1 and 2.

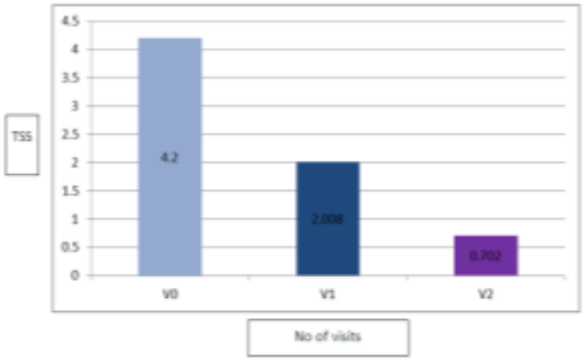

Figure 1: X axis- No of visits, Y axis- Total symptom score.

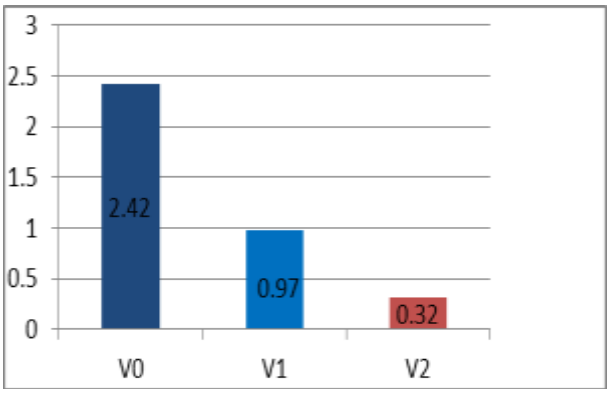

Figure 2: X axis- No of visits, Y axis- Total symptom score

Extrapolating the data to Likert-type symptom scale, at V0 or baseline the mean TSS corresponds to Moderate symptoms which was reduced to Mild in V2 or Day 5.

Safety analysis

The overall incidence of reported study drug related adverse events were **12 seen in 8 patients.** The list of adverse events with the number of episodes is mentioned in Table 2.

Adverse Events	No. of events	No. of patients	% of patients
Ocular Itching	12	8	5.714 %
Total	12	8	5.714 %

DISCUSSION

For the primary care physician, the occurrence of a red eye is a frequent and prominent finding of a disease process in patients. A careful history and simple examination with the observation of typical clinical signs are important for the management of this common disorder.

In the authors knowledge this was the first clinical trial conducted to study the efficacy and safety of a

combination of Phenylephrine, Naphazoline, Menthol, Camphor and Benzalkonium chloride in buffered isotonic aqueous solution.

One of the strongest arm of this clinical study is that the Total Symptom Score is used as a criterion for efficacy assessment and that this data of TSS is extrapolated to Likert-type symptom scale which is the internationally acknowledged scale for assessment of the symptoms. One of the most impressionable thing of the TSS scale lies in the fact that it has 11 grades for the symptom assessment compared to the Likert-type symptom scale which has 4 grades thus increasing the sensitivity of the study. A reduction in Total Symptom score (TSS) in all the patients was observed in the phase IV post marketing surveillance study.

In visit 1, before treating the patient, mean TSS score of ocular Redness and ocular discharge was 4.2 and 2.42 respectively. After treatment with the study medication at day 3, ocular Redness and ocular discharge was reduced to 2.008 and 0.97 respectively. On the 3rd visit after taking the drug combination mean TSS score for ocular redness and ocular discharge was 0.70 and 0.32 respectively. The **TSS reduced** from **4.2 to 2.008** which is reduction of **47.80 %** and from **2.008 to 0.70** which is reduction of **16.66%.** The Total mean symptom score (TSS) was found to reduce at the conclusion visit. i.e. there was a reduction of the mean TSS score of 47.80% and for ocular Redness and ocular discharge respectively.

There was a reduction in the TSS in all the patients in the phase IV post market surveillance study which implies that the study medication was efficacious in treating the ocular Redness condition.

A total of 12 adverse events were observed in 8 patient's i.e in 5% of the patients. The most commonly reported adverse event of mild intensity was ocular itching reported in 5% of the total patients.

The TSS reduced from 4.20 to 2.008 which is reduction of 47.80 % and from 2.94 to 0.71 which is reduction of 24.14%. The Total mean symptom score (TSS) was found to reduce at the conclusion visit i.e. at Visit 3.

Dockhorn RJ et al., conducted a double-masked, randomized, parallel group, placebo-controlled study which demonstrated the efficacy of Naphcon-A (naphazoline HCl 0.025%). Seventy-two patients with a documented positive skin test or radioallergosorbent test were recruited. Three groups of 24 patients each received 1 drop of Naphcon-A instilled in one eye, and 1 drop of naphazoline or placebo in the other eye. After the instillation of test medication, a titrated dose of ragweed antigen was administered bilaterally, and ocular signs and symptoms were evaluated 10, 30, and 120 minutes later. The study concluded with results that showed Naphcon-A was significantly more effective than placebo, naphazoline in reducing redness. Naphcon-A and pheniramine were equally effective in relieving itching.

Vandewalle E[1] et al., conducted a clinical study to check to test whether adding topical phenylephrine 5% to tropicamide 0.5% eye drops in the protocol for pupil dilation affects the retinal vessel oximeter measurements in patients with glaucoma. Also, to test whether phenylephrine 5% has an influence as a vasoconstrictor on the retinal vessel width and can improve the proportion of high-quality retinal images in patients with glaucoma. Retinal images of 66 patients with chronic open-angle glaucoma were obtained before and after the administration of phenylephrine 5% eye drops to patients already dilated with tropicamide 0.5% with the Oxymap Retinal Oximeter (Oxymap ehf, Reykjavik, Iceland).The study showed The addition of topical phenylephrine 5% after tropicamide 0.5% improved the proportion of high-quality retinal oximetry images without influencing the retinal oxygen saturation values or the retinal vessel diameter in patients with glaucoma.

Xu X[1]et al conducted a clinical trial to assess the safety and effectiveness of menthol as a permeability enhancer in ophthalmic drug delivery systems. In this study, the effect of menthol on permeability of dexamethasone disodium phosphate in the cornea and sclera was investigated in vitro. The present study shows that menthol may improve the ocular penetration of a drug in a transcorneal and transscleral drug delivery system without causing toxic reactions.

A study presented the case of a 56-year-old man with blepharoconjunctivitis after instillation of phenylephrine 5%, tropicamide 0.5%, oxibuprocaine eyedrops. The patient reported good tolerance to the mentioned drugs. Immediate readings of prick and intradermal tests, performed with the suspected drugs, were negative. Late readings (48 and 72 hours) of epicutaneous tests were also negative. At 72 hours, prick and intradermal tests to phenylephrine were positive. Allergic blepharoconjunctivitis to phenylephrine was diagnosed. Phenylephrine is an extensively used midriatic that can act as a potent sensitizing agent and can be the cause of allergic contact reactions in exposed patients. With this case we illustrate the relevance of late readings of intradermal tests in the diagnosis of late hypersensitivity drug reactions. The authors discuss about possible mechanisms responsible for negative results of epicutaneous tests.

CONCLUSION

A combination of Phenylephrine and Naphazoline is considered to be safe and provides symptomatic relief for the treatment of ocular Redness and ocular itching.

Disclosure : This study is done for Ocurest Eye Drops from Centaur Pharmaceuticals Pvt Ltd.

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