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Safety and Efficacy of a Combination of Chloramphenicol, Polymyxin-B and Dexamethasone in Ocular Infection with Inflammation

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Abstract:

Introduction: *Ocular infection with inflammation is very common in developing countries like India. Multi-drug therapy is used in the treatment of Ocular infection with inflammation. We studied the safety as well as efficacy of one such combination anti-bacterial (Chloramphenicol and Polymyxin -B) and corticosteroid (Dexamethasone) in the treatment of Ocular infection with inflammation especially mild keratitis and conjunctivitis.* ***Methodology:*** *Out of 151 patients, 117 were completed the study. Efficacy assessment was made by reduction in Visual Analogue Scale (VAS) Score of Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis related to Ocular infection with inflammation. Safety assessment was made by inspecting the adverse events during the study.* ***Results:*** *Reduction in mean VAS score was analysed from 4.47 (baseline) to 2.76 (day 3) to 0.55 (day 5) of ocular hypermia, from 3.42 (baseline) to 2.03 (day 3) to 0.24 (day 5) of ocular discharge, 3.57 (baseline) to 1.89 (day 3) to 0.21 (day 5) of keratitis and from 3.84 (baseline) to 2.10 (day 3) to 0.20 (day 5) of conjunctivitis. Majority of patients had more than 90% reduction in their VAS score at conclusion visit in all the parameters. 8.54% of adverse events of mild intensity was observed.* ***Conclusion:*** *A fixed dose combination of Chloramphenicol, Polymyxin-B and Dexamethasone of is safe and effective in the treatment of Ocular infection with inflammation.*

Keywords: ***Chloramphenicol, Polymyxin-B, Dexamethasone, Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis.***

Introduction:

The eye is necessary and a unique organ which has a constant exposure to the environment.[1] Ocular infection with inflammation involve any part and surrounding tissues of the eye.[2] Many of the bacteria, viruses, parasitic pathogens, and fungi can cause systemic infection and are capable of infecting the interior or surface of the eye.[3] The most common ocular infection are Conjunctivitis, Keratitis, Blepharitis, Meibomitis, and Endophthalmitis.[4]

Bacterial Conjunctivitis is an inflammation or infection of the conjunctiva, a thin protective membrane which covers the front white mucous membrane of the eye and inner periphery of the eyelids. Most commonly conjunctivitis is caused by bacteria, virus and sometimes allergy. The common symptoms are redness of eyes and watering, produce yellowish white discharge that makes eyelids to stick together, strong itching, burning sensation and headache.[5,6] Keratitis is a serious ocular infectious disease termed for inflammation of cornea which is caused by injury of the corneal tissue, bacterial or fungal contamination of contact lenses which can pass into cornea. Keratitis can cause painful inflammation of cornea, corneal discharge, or leads to severe visual disability[4,7] Blepharitis involves infection with inflammation of the eyelid margin. The inflamed eyelids shows hyperaemia with scaling, collarettes, and crusting on the eyelashes. Chronic bacterial Blepharitis infection leads to loss of eyelashes. Blepharitisconjunctivitis is a condition where conjunctiva gets involve due to Blepharitis.[4] Meibomitis is Meibomian Gland inflammation also known as Posterior Blepharitis which effects the inner eyelid margin. Meibomian Gland produces oil to prevent evaporation of tears, dysfunctioning of Meibomian Gland leads to inflammation or dry eyes.[8,9] Endophthalmitis is a bacterial or fungal infection in the vitreous humors located in the eye. Bacterial Endophthalmitis can occur by direct or surgical injury cause inflammation of vitreous gel which leads to visual disability or even permanent loss of vision.[4,10]

In India, the exact incidence and prevalence of bacterial conjunctivitis is not known clearly. However the international data estimates the prevalence of bacterial conjunctivitis in United States as 1.37% per year. Bacterial conjunctivitis are around 50 to 70% of all conjunctivitis cases which include both gram positive organism such as *Staphylococcus aureus* (31%) and *Staphylococcus pneumonia* (16%) as well as gram negative organism *Pseudomonas aeruginosa* (10%) and *Klebsiella* (8%).[11]

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Chloramphenicol is a first broad-spectrum, semisynthetic antibiotic which acts by blocking bacterial protein synthesis mainly has bacteriostatic activity but at higher doses it is bacteriocidal. It diffuses through the bacterial cell wall and reversibly binds to 50s ribosomal subunit of the bacterial. The binding restrain the peptidyl transferase activity and prevents incorporation of amino acids to the developing peptide chains and thus, it blocks the peptide bond formation. As a result, Chloramphenicol blocks the synthesis protein and prevent cell proliferation of the bacteria.[12,13,14] Polymyxin-B is rapidly acting bactericidal for gram negative bacteria having detergent like action on the bacterial cell membrane. It has positive affinity towards phospholipids. The peptide aggregates or molecules place between the protein films in bacterial cell membrane and phospholipids. It promotes distortion of bacterial cell membrane and formation of psuedopore, causes amino acids leakage which leads to bactericidal activity against gram negative bacteria especially *Pseudomonas aeruginosa*.[15,16] Dexamethasone ophthalmic is a corticosteroid. It inhibit the process that cause inflammation. It decreases the swelling, pain of inflammation caused by infection, injury, surgery or other conditions. It was also found to preserve clarity of the cornea and wound healing of cornea associated with dry eyes.[17]

The combination of Chloramphenicol, Polymyxin-B and Dexamethasone is used for treatment of ocular bacterial infection with inflammation in the eye. The combination of these three drugs are readily available in market and are popular for its use in ocular bacterial infection with inflammation. However there is a shortfall of clinical data for this combination therefore a Phase IV or Post-marketing study has conducted to document the safety and efficacy of Chloramphenicol, Polymyxin-B and Dexamethasone in the treatment of ocular bacterial infection with inflammation.

Methodology

The phase IV clinical trial was conducted in 12 ophthalmology center in various cities all over India. The study period was from February 2017 to May 2017. A total number of 151 patients were enrolled for the study, out of which 117 patients completed and 34 patients were lost to follow-up.

Inclusion and exclusion study

Patients with confirmed diagnosis of ocular infection with inflammation were included in the study. The study included patients of both gender between the ages of 18 to 75 years. Only the patients who were strictly cohere to the protocol were recruited for the study. Patients with hypersensitivity to the individual study drug or to any of its ingredients were excluded from the study. Glaucoma or any other eye condition patients were excluded from the study. Lactating mothers, pregnant womens and mentally ill were also excluded from the study.

Study intervention

Study drug- Drops containing FDC of Chloramphenicol 4 mg, Polymyxin-B 5000 I.U. and Dexamethasone 1 mg per ml, Ointment containing FDC of Chloramphenicol 4 mg, Polymyxin-B 5000 I.U. and Dexamethasone 1 mg per mg. One 4 ml bottles of drops and 5 gm tube of study medication provided to patients at free of cost respectively. All the samples were dispensed by the investigator to the patient. The study dosage and administration- patients were ask to instill 1-2 drops of Ocupol Dx Eye drop twice or thrice a day during day time and half an inch of Ocupol Dx Ointment before sleeping for a study period of 5 days.

Study procedure

Only registered ophthalmologists were involved as an investigators for conducting this study. The study duration for eye drops and ointment was kept 5 days to determine the safety and efficacy of both the combination. Patients suffering from Ocular Inflammation and Infection who are satisfying the inclusion/exclusion criteria were enrolled for the study. A detailed medical history was obtained from each patient through clinical examination. Patients were dispensed with 4 ml bottle of Ocupol Dx Eye Drops and 5 gm tube of Ocupol Dx Eye Ointment free physician samples and were ask to instill 1-2 drops of Ocupol Dx Eye drop twice or thrice a day during day time and half an inch of Ocupol Dx Ointment before sleeping for a study period of 5 days. Patient were asked to maintain a diary to record any adverse events occurring during the study duration.

Three visits were planned for all the patients enrolled in this study – the first visit V1 (baseline visit) on day 1 before treating patient with the study drug medication, the second visit V2 (revaluation visit) on day 3 and the third visit V3 (last or conclusion visit) on day 5. Adverse events occurring and VAS score were recorded at each visit along with medical history and clinical examination. Patients were instructed to keep a daily note of symptoms and any adverse effect occurring during the study duration. In case of the investigator observe any safety-related issues and adverse events or serious adverse events, the investigator can withdraw the patient from the study and treat according to the severity of the symptoms.

Concomitant therapy

No Pharmacological or Non- pharmacological interventions and medications were permitted for use during the study duration of 5 days.

Efficacy assessment

The primary assessment was the reduction in the VAS score for the Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis related to Ocular inflammation and infection on an (0 to 10) eleven-point scale where 0 refer to no

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symptoms i.e. completely cured patients and 10 refer to maximum tolerated symptoms. The secondary assessment was the percentage reduction in mean VAS score of Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis at visit 2 and visit 3 as compared to baseline.

Safety assessment

Patients were interrogated for any adverse event at all the visit and if present were recorded in the case record form (CRF) during all the visit. The adverse events were classified into serious and non-serious adverse events. Naranjo's scale of probability was used to classify the adverse event as drug related or non-drug related. Adverse events were followed up and also treated if necessary by the investigators till the symptoms abate.

Regulatory matters

In India, this combination is available and classified under schedule 'H' drug, therefore it should be sold in the presence of prescription of a registered medical practitioner only. All the participated patients in the study have read and signed the Inform consent form (ICF). The combination for Eye drops containing FDC of Chloramphenicol 4 mg, Polymyxin-B 5000 I.U. and Dexamethasone 1 mg per ml and Eye Ointment, FDC of Chloramphenicol 10 mg, Polymyxin-B 10000 I.U. and Dexamethasone 1 mg per gm, is approved by DCGI office (Drug Controller General of India), Central Drugs Standard Control Organization (CDSCO) under serial no. 1419 for drops and 141 for ointment.

Results

A total number 151 patients were recruited at 12 ophthalmologist speciality center across India. 117 patients completed the study and were analysed.

Efficacy Analysis

The Mean of VAS score of Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis at each visit was evaluated and individually plotted graphically as shown in figure no. 1. The Percent reduction in mean VAS score in Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis at visit 2 and visit 3 was evaluated and individually plotted in figure no. 2. At baseline the mean VAS score for Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis was 4.47, 3.42, 3.57 and 3.84 respectively. On visit 2 i.e. day 3 after taking study drug combination the mean VAS score for Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis was reduced to 2.76, 2.03, 1.89 and 2.10 respectively. At visit 2 the percentage reduction in mean VAS score for Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis was found out to be 38.25%, 40.64 %, 47.50 % and 45.31%. On visit 3 i.e. day 5 the mean VAS score of Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis was further reduced to 0.55, 0.24, 0.21 and 0.28 respectively. Similarly at visit 3 the percentage reduction of Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis was found out to be 81.69%, 92.98%, 94.11% and 91.71% in mean VAS score.

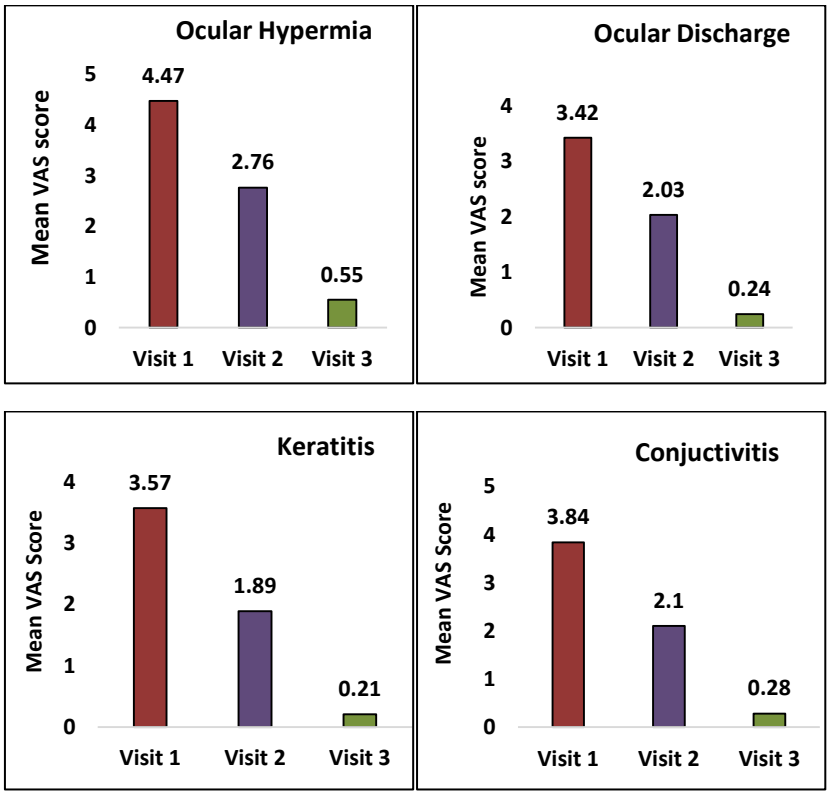

Fig no. 1 Reduction in mean VAS score in Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis at each visit

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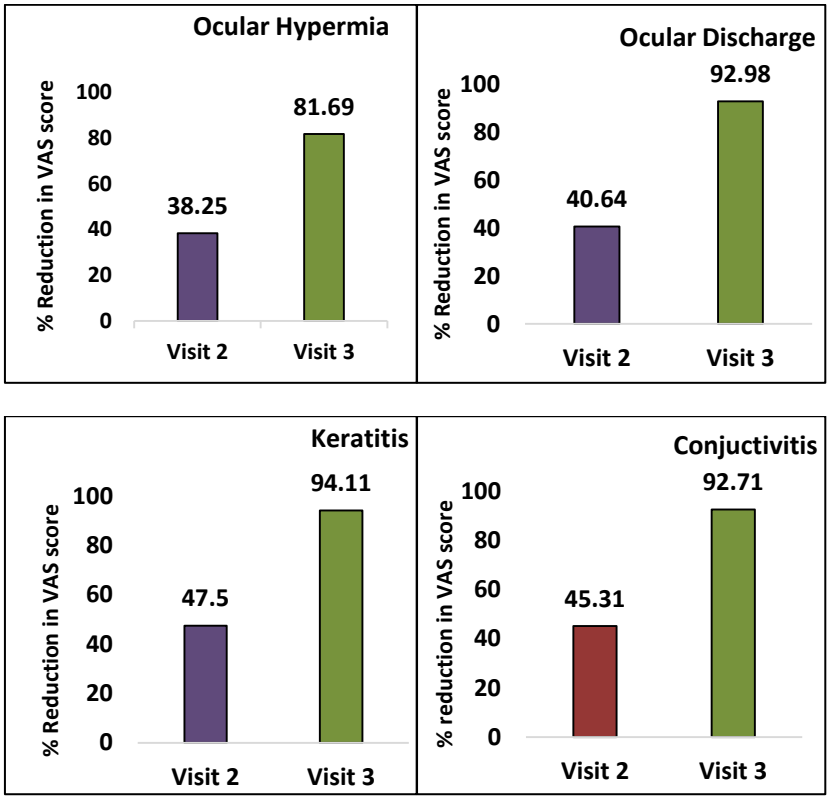

Fig no. 2 Percentage reduction in mean VAS score Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis at each visit

Safety Analysis

The overall incidences of reported study drug related adverse events were 30 seen in 10 patients. The list of adverse events with the number of episodes is mentioned in Table no. 1

Table no. 1: Adverse events, no. of episodes, no. of patients and percentage of patients experience from total population.

Adverse event	No. of episodes	No. of patient	Percentage of patients
Mild Burning Sensation	13	6	5.12
Mild Itching	7	3	2.56
Mild Irritation	10	7	5.98
Total	**30**	**10**	**8.54**

Discussion

Ocular inflammation and infection is the significant health complication worldwide that impacts greatly on daily life and routine. The clinical management of Ocular inflammation and infection depends on the part infected and pathogen involved for infection with inflammation of the eye.

In the best of all the author's knowledge, this is the first clinical trial or Post marking study (PMS) conducted for the safety and efficacy analysis of the combination of Chloramphenicol, Polymyxin-B and Dexamethasone in treatment of Ocular inflammation and infection. Strong arm of this clinical study is Visual Analogue Scale (VAS) used for efficacy analysis. VAS has 11 grades for symptom assessment which makes the VAS more susceptible and sensitive. VAS is used for analysing the main and common symptoms of Ocular inflammation and infection which are Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis at all the visits so that we could analyse the safety and efficacy of the study drug medication.

In baseline visit (V1) before treating patient, it was found that the mean VAS score of Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis was 4.47, 3.42, 3.57 and 3.84 respectively. After medication at re-evaluation visit (V2) i.e. day 3, the mean VAS score for Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis was reduced to 2.76, 2.03, 1.89 and 2.10 and the percentage reduction in mean VAS score was found out to be 38.25%, 40.64 %, 47.50 % and 45.31% respectively. At Conclusion visit (V3) i.e. day 5, the mean VAS score of Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis was further reduced to 0.55, 0.24, 0.21 and 0.28 and similarly the percentage reduction was found out to be 81.69%, 92.98%, 94.11% and 91.71% respectively in mean VAS score. Thus study drug medication was found to be efficacious in treating Ocular

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inflammation and infection which include Ocular hypermia, Ocular discharge, Keratitis and Conjunctivitis.

Total 30 adverse events incidences were observed in 10 patients i.e. in 8.54 % of patients. The adverse events observed were of mild intensity including burning sensation (in 5.12 % of patients), mild itching (in 2.56 % of patients) and mild irritation (in 5.98 % of patients).

The most common bacterial species isolated for ocular inflammation and infection are both gram positive organism such as *Staphylococcus aureus* and *Staphylococcus pneumonia* as well as gram negative organism *Pseudomonas aeruginosa* and *Klebsiella.* The in-vitro susceptible testing for ocular infection was done in South India by using a common antibacterial Chloramphenicol which was found to be highly efficacious towards gram positive bacteria. Chloramphenicol shows susceptibility against *Staphylococcus aureus (*87%) and *Staphylococcus pneumonia* (77%). Chloramphenicol has less efficacy towards gram negative bacteria compared to gram positive. Its susceptibility against *Pseudomonas aeruginosa* (31%) and *Klebsiella* (63%). Therefore Chloramphenicol with Polymyxin-B in combination is highly effective against gram positive as well as gram negative bacteria.[18]

Bacterial keratitis is one of the most visually threatening ocular inflammation and infection. A prospective clinical and microbial study was done in Swiss Eye Hospital in different patients for 21 months and it was found that the most common isolated gram positive bacteria is *Staphylococcus* species whereas *Pseudomonas aeruginosa* the most encountered gram negative bacteria. It was found that Chloramphenicol was 100% sensitive for all gram positive bacteria whereas Polymyxin-B was 13% sensitive. For all gram negative bacteria Chloramphenicol is 35% sensitive whereas Polymyxin-B was 82% sensitive. This study was performed to test the bacteria against the antibiotics which are most commonly used in order to frame a new guidelines for the ocular therapy.[19]

The clinical study was design to evaluate the safety and efficacy of fixed-combination eye drop (moxifloxacin 0.5%/dexamethasone 0.1%) versus concomitant moxifloxacin 0.5% and dexamethasone 0.1% ocular solutions for the treatment of bacterial ocular infection with inflammation. In this study clinical resolution, symptoms, signs, and safety were assessed at each visit. The clinical resolution was found out to be similarly in both groups i.e. 81.6% for fixed-dose group and 82.3% of concomitant group. Ocular signs and symptoms improved, with no statistical differences between groups after the treatment of 7 days. The fixed-dose group had significantly more eyes with clinical resolution in eyelid erythema i.e. (100%) fixed-dose group and (92.7%) concomitant group; $P = 0.0194$) and eyelid scaling/crusting (98%) fixed-dose group and (89.6%) concomitant group; $P = 0.0337$). Five adverse event in fixed-combination group and six adverse event in concomitant group were reported which include moderate case of burning sensation, mild increase in IOP and sleeplessness. Both treatment of regimens were found to be safe, efficacious and well tolerated in patients with bacterial ocular infection with inflammation.[20]

In the entire study, No microbial count study was performed. In bacterial conjunctivitis or keratitis microbial count studies are not routinely conducted. The study was completely based on clinical cure.

Conclusion

The combination of Chloramphenicol, Polymyxin-B and Dexamethasone was found to be efficacious as well as safe in treatment of Ocular infection with inflammation.

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Conflict of Interest - None

Disclosure

This study was conducted as a part of Pharmacovigilance activity for Ocupol Dx Eye Drops and Ocupol Dx Ointment by Centaur Pharmaceuticals Pvt Ltd. in accordance with Pharmacovigilance Program of India (PvPI).

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