Evaluation of efficacy and safety of Ophthacare eye drops in acute and chronic conjunctivitis

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ABSTRACT

Most conjunctival disorders are self-limiting and seldom affect vision, but some may lead to blindness, if left untreated. The available treatment options have some drawbacks, which limit their use in clinical practice. Though mild or moderate cases of infectious conjunctivitis are treated with topical antimicrobials, viral conjunctivitis remains a major problem in clinical practice and the trend of increasing incidence of multi-drug resistance bacterial conjunctivitis is emerging as an area of concern. Various research studies have demonstrated the effectiveness of polyherbal formulations in management of acute and chronic conjunctivitis and this study was planned to evaluate the efficacy and safety of Ophthacare eye drops in the same.

This was an open non-comparative clinical trial and one hundred and sixteen patients with clinical symptoms of acute and chronic conjunctivitis, who were willing to give informed consent, were enrolled in the study. Patients with predominant keratitis, corneal ulcer, uncontrolled keratoconjunctivitis sicca, glaucoma, diabetes and hypertension were excluded from the study.

A detailed past medical history and history of present symptoms was obtained from all patients. All patients underwent a thorough ophthalmic examination with special emphasis on objective signs such as discharge, congestion, follicle in the eyes, papillae and lid swelling. Discharge status, congestion, presence of papillae and follicles in the eyes, lid swelling and feeling of gritty sensation were selected parameters for the objective monitoring. The mean conjunctivitis score was calculated by addition of individual scores of discharge status, papillae, follicle in the eyes, lid swelling, gritty sensation and congestion. All patients suffering from acute conjunctivitis were advised to instil Ophthacare eye drops two drops in both eyes, every two hours for a week, while all patients suffering from chronic conjunctivitis were advised to instil two drops in both eyes four times a day for 15 days.

Patients were followed up every third day (days 3, 6, 9, 12 and 15). All adverse events either reported or observed by patients were recorded in a structured CRF Case Record Format (CRF) with information about severity, date of onset, duration and action taken regarding the study drug. Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. The predefined primary end points were subjective symptomatic relief and objective clinical improvement. The predefined secondary end points were the duration required for the clinical cure and incidence of any short- and long-term adverse event. Statistical analysis was done according to intention-to-treat principles. Changes in various parameters from baseline values and values after 15 days, were analyzed by “paired t test”.

Statistical analysis was done according to intention-to-treat principles. Changes in various parameters from baseline values and values after 15 days, were analyzed by “paired t test”.
The minimum level of significance was fixed at 99% confidence limit and a 2-sided p value of <0.0001 was considered significant.

There was a significant reduction in the mean score for conjunctivitis, congestion, papillae and follicle at the end of the study period. There were no clinically significant adverse events either observed or reported, except for mild local allergic manifestations seen in two patients. Ophthacare eye drops are clinically beneficial in the management of acute and chronic conjunctivitis by the synergistic (anti-inflammatory, antimicrobial, antioxidant, immunostimulatory and antiallergic) actions of its ingredients. Therefore it may be concluded that Ophthacare eye drops are clinically efficient and safe in the management of acute and chronic conjunctivitis.

INTRODUCTION
Most conjunctival disorders are self-limiting and seldom affect vision, but some may lead to blindness, if left untreated. Conjunctivitis is characterized by hyperemia of the conjunctiva, transmitted by contaminated fomites or the patient's own hands, and spreads rapidly from one eye to the other. Acute bacterial conjunctivitis lasts about two weeks and viral conjunctival infections may last for two to three weeks, whereas other types of conjunctivitis follow a chronic course producing considerable disability. Chronic conjunctivitis is an indication of degenerative changes or damage from repeated acute attacks. Conjunctivitis can be due to allergens, infections (bacterial, fungal or viral) parasitic infestation. An idiopathic form of conjunctivitis may be associated with certain systemic diseases (erythema multiforme and thyroid disease) and it may also be secondary to pneumococcal dacryocystitis or candidal canaliculitis.

The available treatment options have some drawbacks, which limit their use in clinical practice. Though mild or moderate cases of infectious conjunctivitis are treated with topical antimicrobials, viral conjunctivitis remains a major problem in clinical practice and the trend of increasing incidence of multi-drug resistance bacterial conjunctivitis is emerging as an area of concern.

Various research studies have demonstrated the effectiveness of polyherbal formulations in management of acute and chronic conjunctivitis\(^1\text{--}\text{4}\). Ophthacare eye drops is a polyherbal formulation indicated for acute and chronic conjunctivitis and it contains extracts of *Carum copticum*, *Terminalia bellirica*, *Emblica officinalis*, *Curcuma longa*, *Ocimum sanctum*, *Rosa damascena*, *Cinnamomum camphora* with purified *Mel despumatum* (Honey). This study was planned to evaluate the efficacy and safety of Ophthacare eye drops in acute and chronic conjunctivitis.

**Aim of study**
The present study was planned to evaluate the clinical efficacy and safety of Ophthacare eye drops, on topical application, in acute and chronic conjunctivitis.

**Study Design**
This was an open non-comparative clinical trial, conducted from July-December 2003.

**MATERIAL AND METHODS**
**Inclusion Criteria**
One hundred and sixteen patients with clinical symptoms of acute and chronic conjunctivitis, who were willing to give informed consent, were enrolled in the study.

**Exclusion Criteria**
Patients with predominant keratitis, corneal ulcer, uncontrolled keratoconjunctivitis sicca and evidence of glaucoma, diabetes and hypertension were excluded from the study.

**Study Procedures**
Total one hundred and sixteen patients (55 females and 61 males), in the age range of 12 to 87 years were enrolled in the study. A written informed consent was obtained from all patients, (from the guardian of the patient, where the patient was a minor). A detailed past medical history and history of present symptoms was obtained from all patients. All patients underwent a through ophthalmic examination with special emphasis on objective signs as discharge, congestion, follicle, papillae and lid swelling.

If the duration of conjunctivitis symptoms in the enrolled patient was less than a week, then the patient was classified as “acute case of conjunctivitis” and if the same was more than a week, then the case was classified as “chronic case of conjunctivitis”.

Discharge status, congestion, presence of papillae and follicles in the eyes, lid swelling and feeling of gritty sensation were selected parameters for the objective monitoring. The discharge status rating was done as: no discharge (0), watery discharge (1), mucoid discharge (2) and mucopurulent discharge (4). The score for congestion was predefined as: no congestion (0), mild congestion (1), moderate congestion (2) and severe congestion (3). If there were no papillae the rating was “0”, if the number of papillae was less than 5, it was rated as ‘1’ and if the number of papillae was more than 5, it was rated as ‘2’. If there were no follicles the rating was “0”, if the number of follicles was less than 5, it was rated as ‘1’, and if the number of follicles was more than 5, it was rated as ‘2’. The status of lid swelling was rated as: absent (0), mild swelling (1), moderate swelling (2) and unable to open eyes (3). If the patient was not experiencing gritty sensation, it was rated ‘0’, and if the patient was experiencing gritty sensation, it was rated ‘1’.

The mean conjunctivitis score was calculated by addition of individual scores of discharge status, papillae, follicle, lid swelling, gritty sensation and congestion. Mean conjunctivitis scores reflected the severity of the conjunctivitis as: total score below 3 (mild conjunctivitis), total score between 4 to 7 (moderate conjunctivitis) and total score above 8 (severe conjunctivitis). Mean conjunctivitis score indicated the collective evaluation of both, subjective and objective improvement in disease status.

All patients suffering from acute conjunctivitis were advised to instil Ophthacare eye drops, two drops, in both eyes, every two hours, for a week, while all patients suffering from chronic conjunctivitis were advised to instil two drops in both eyes four times a day for 15 days.

**Follow-up and assessment**
All patients were followed up on every third day (days 3, 6, 9, 12 and 15). At each follow up visit, patients were evaluated for symptomatic relief and for any adverse event/s such as hypersensitivity, burning, itching sensation or pain.
**Adverse events**

All adverse events either reported or observed by patients were recorded in a structured case record format (CRF) with information about severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to study medication was predefined as “Unrelated” (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), “Possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and “Probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

**Primary and secondary end points**

The predefined primary end points were subjective symptomatic relief (reduction in lacrimation, eye pain, redness of the eyes, gritty feeling in the eye, itching of the eye, blurred vision, discharge from the eyes, and sensitivity to light) and objective clinical improvement. The predefined secondary end points were the duration required for the clinical cure and incidence of any short- and long-term adverse event.

**Statistical analysis**

Statistical analysis was done according to intention-to-treat principles. Changes in various parameters from baseline values and values after the 15 days, were analyzed by “paired ‘t’ test”. The minimum level of significance was fixed at 99% confidence limit and a 2-sided p value of <0.0001 was considered significant.

**RESULTS**

Total 116 patients (230 eyes, as all but two patients had bilateral conjunctivitis) were evaluated to assess the response of Ophthacare eye drops. At the time of enrollment in the study, 39 patients had acute conjunctivitis and 77 patients had chronic conjunctivitis.

Out of 116 patients significant improvement was observed in 85 (73.18%) patients. There was a significant reduction in the mean score for conjunctivitis from a value of 5.224 to 0.5412, at the end of the study period (n=85, mean of differences = 4.682, 99% confidence interval=4.416 to 4.949, t=46.49, df=84, p<0.0001, significant) (Figure 1). There was significant reduction in the mean score for congestion also, from a value of 108 to 3, at the end of the study period (n=85, mean of differences = 1.235, 99% confidence interval = 0.9749 to 1.496, t=12.54, df=84, p<0.0001, significant) (Figure 2). A significant reduction in the mean score for papillae from a value of 71 to 20, was observed at the end of the study period (n=85, mean of differences = 0.6000, 99% confidence interval = 0.3127 to 0.8873, t=5.519, df=84, p<0.0001, significant) (Figure 3) and similarly, there was a significant reduction in the mean score for follicles from a value of 49 to 9, at the end of the study period (n=85, mean of differences = 0.4706, 99% confidence interval = 0.2341 to 0.7071, t=5.259, df=84, p<0.0001, significant) (Figure 4).
There were no clinically significant adverse events either observed or reported, except for mild local allergic manifestations seen in two patients.

**DISCUSSION**

The conjunctiva is a loose connective tissue that covers the surface of the eyeball (bulbar conjunctiva) and reflects back upon itself to form the inner layer of the eyelid (palpebral conjunctiva). The conjunctiva firmly adheres to the sclera at the limbus, where it meets the cornea. The accessory lacrimal glands, along with goblet cells, are situated within the conjunctiva and are responsible for keeping the eye lubricated. As with any mucous membrane, infectious agents may adhere to the conjunctiva, thus overwhelming normal defense mechanisms and producing clinical symptoms of conjunctivitis (redness, discharge, irritation, and possibly photophobia). The clinical term "red eye" is applied to a variety of distinct infectious or inflammatory ocular disease processes that involve one or more tissue layers of the eye, and the term "conjunctivitis" encompasses a broad group of conditions presenting as inflammation of the conjunctiva. The inflammation can be hyperacute, acute or chronic in presentation, and infectious or noninfectious in origin.5

The clinical findings and course of conjunctivitis is influenced by the causing pathogen, and it usually presents with hyperemia and discharge. Pain is minimal and the visual acuity is slightly reduced, and the cornea may be involved with inflammatory leukocytic infiltrations with superficial vascularization. Both endemic trachoma and adult inclusion conjunctivitis is
characterized by small lymphoid follicles in the conjunctiva. Adult inclusion conjunctivitis presents as the acute onset of unilateral follicular conjunctivitis and preauricular lymphadenopathy and if untreated, the disease may persist for years. Adenovirus infection causes a watery discharge, mild foreign-body sensation, and photophobia. Assessing the time course, the morphologic appearance of conjunctiva, type of exudate and most severely affected area of conjunctiva are critical factors in acute conjunctivitis.

Cultures usually are not required in patients with mild conjunctivitis of suspected viral, bacterial or allergic origin. However, specimens for bacterial cultures are obtained in patients who have severe inflammation (e.g., hyperacute purulent conjunctivitis) or chronic recurrent conjunctivitis. Conjunctival cytology scrapings for Gram staining and/or Giemsa staining help to characterize the conjunctival inflammatory response and these findings are helpful, particularly for diagnosing allergic, chlamydial and atypical forms of conjunctivitis, in which the clinical diagnosis is not immediately apparent. Several laboratory procedures (cell culture, direct fluorescent monoclonal antibody staining of smears, enzyme immunoassays, DNA hybridization assays and a polymerase chain reaction test) are available to identify specific antigens.

Hyperacute bacterial conjunctivitis is a severe, sight-threatening ocular infection with an abrupt onset and is characterized by a copious yellow-green purulent discharge that reaccumulates after wiping. The most frequent causes of hyperacute purulent conjunctivitis are Neisseria gonorrhoeae and Neisseria meningitidis, and these two infections have similar clinical presentations, which can be distinguished only in a microbiology laboratory. Gonococcal ocular infection usually presents in neonates (ophthalmia neonatorum) and affected infants typically develop bilateral discharge three to five days after birth. Transmission of the Neisseria organism to infants occurs during vaginal delivery and in adults, the organism is usually transmitted from the genitalia to the hands and then to the eyes. The three most common pathogens in bacterial conjunctivitis are Streptococcus pneumoniae, Hemophilus influenzae and Staphylococcus aureus. Although acute bacterial conjunctivitis is usually self-limited and does not cause any serious harm, there are several justifications for treatment, which include decreasing morbidity by shortening the course of the disease, reducing person-to-person transmission, lowering the risk of sight-threatening complications (corneal ulceration) and eliminating the risk of more widespread extraocular disease. Unfortunately, no single broad-spectrum antibiotic covers all potential conjunctival bacterial pathogens. Furthermore, some are associated with a relatively high incidence of toxicity to the corneal epithelium, with prolonged use and some can cause local oculocutaneous adverse reactions.

Chronic bacterial conjunctivitis is most commonly caused by Staphylococcus species and it develops in association with blepharitis, which is a common inflammatory condition of the eyelid margins. Some patients with chronic bacterial conjunctivitis also have recurrent styes and chalazia (lipogranulomas) of the lid margin. The meibomian glands are sebaceous glands that line the posterior lid margin behind the eyelashes and these glands secrete an important oily component of the tear film. When inflamed, the meibomian glands malfunction, producing chronic inflammation of the eyelid margins and the conjunctiva, as well as irritating dry-eye symptoms (meibomianitis). Trachoma, a chronic keratoconjunctivitis, is the most common cause of ocular morbidity and preventable blindness throughout the world. It is a major public health concern in the rural areas of developing countries. Inclusion conjunctivitis is a common, primarily sexually transmitted disease that occurs in both newborns (ophthalmia neonatorum) and adults.
Adenovirus and herpes simplex virus are the most common causes of viral conjunctivitis and in such patients; topical corticosteroid therapy can lead to severe ocular complications as a result of uncontrolled virus proliferation. Furthermore, topical corticosteroid therapy places the patient at risk for other steroid-induced ocular complications, such as glaucoma and cataracts. Ocular infections due to herpes simplex and herpes zoster are becoming more prevalent as the incidence of human immunodeficiency virus infection continues to increase.

Ocular allergy in its many forms is one of the major causes of chronic conjunctivitis and it encompasses a spectrum of distinct clinical conditions. Itching is the hallmark of allergic conjunctivitis, as well as other forms of allergic eye disease. The most common of these allergic conditions is seasonal allergic rhinoconjunctivitis (hay fever rhinoconjunctivitis), which is an IgE-mediated hypersensitivity reaction. Patients typically experience intermittent bouts of itching, tearing, redness and mild eyelid swelling and the personal or family history is often positive for other atopic conditions, such as allergic rhinitis, asthma or eczema. Blepharitis (inflammation of the eyelid margin), dry eye and the prolonged use of ophthalmic medications, contact lenses and ophthalmic solutions are also relatively frequent causes of chronic conjunctival inflammation.

A serous discharge is most commonly associated with viral or allergic ocular conditions and a mucoid discharge is highly characteristic of allergy. A mucopurulent or purulent discharge, often associated with morning crusting and difficulty opening the eyelids, strongly suggests a bacterial infection. The possibility of Neisseria gonorrhoeae infection must be considered when the discharge is copiously purulent. Pain and photophobia are not typical features of a primary conjunctival inflammatory process, but their presence indicates more serious underlying ocular or orbital disease processes (uveitis, keratitis, acute glaucoma and orbital cellulitis). Viral or chlamydial inclusion conjunctivitis typically presents with a small, tender, preauricular or submandibular lymph node and toxic conjunctivitis secondary to topical medications can also produce a palpable preauricular node.

This study observed a significant reduction in the mean score for conjunctivitis, congestion, papillae and follicle in the patients with acute and chronic conjunctivitis. There were no clinically significant adverse events observed or reported during the study period. These results are comparable to earlier clinical trial’s results with Ophthacare eye drops. These results might be due to the synergistic actions of the ingredients of Ophthacare eye drops.

The principle ingredients of Emblica officinalis are tannoids (emblicanin A and B, punigluconin, and pedunculagin) and Emblica officinalis has a potent anti-inflammatory property. Khanom et al. identified the strong superoxide-scavenging and prolyl endopeptidase inhibitory activity of Emblica officinalis. Sai Ram et al. observed that Emblica officinalis significantly inhibited free radical production, restored the antioxidant status, relieved the immunosuppressive effects on lymphocyte proliferation, and restored the IL-2 and gamma-IFN production. One study reported that Emblica officinalis enhanced cell survival, decreased free radical production and higher antioxidant levels, inhibited induced immunosuppression and restored both phagocytosis and gamma-IFN production by macrophages. In another study, immunosuppression in the early phase with mild hyperplasia, infiltration of few mononuclear cells and decrease in the induction of nitric oxide synthase was observed with Emblica officinalis.
Curcuminoids, a group of phenolic compounds isolated from Curcuma longa, have anti-inflammatory, antioxidant and antimicrobial activities\(^{23}\). Curcumin has been shown to inhibit a number of molecules involved in inflammation (phospholipase, lipoxygenase (LO), cyclooxygenase (COX) 1 & 2, leukotrienes (LT), thromboxane (TX), prostaglandins (PG), NO, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1 (MCP-1), interferon-inducible protein, TNF, and interleukin (IL)\(^{12,24,25}\). In a study, the antioxidant effect of curcumin was demonstrated, and it was postulated that the antioxidant actions of curcumin were due to inhibition of Ca2+ entry and PKC activity\(^{26}\). Hong et al. demonstrated that the active extract of Curcuma longa mediates COX-2 and possesses iNOS inhibitory activities\(^{25}\). Curcumin inhibits LO1 by binding to its central cavity\(^{27,28}\), and it also inhibits suppression of COX-2 expression by inhibiting ERK activity and NF-kappaB activation, which represent its molecular mechanisms\(^{29}\). In vitro, curcumin inhibited LPS-induced production of TNF and IL-1 by monocytic macrophages\(^{30}\). Kang et al. observed that curcumin significantly inhibited production of IL-12, reduced induction of IFN-gamma, and IL-4 in CD4+ T cells by macrophages, leading to the inhibition of Th1 cytokine profile (↓ IFN-gamma and ↑ IL-4 production) in CD4+ T cells\(^{31}\). Curcuma longa has an anti-inflammatory activity, which is comparable to hydrocortisone acetate and phenylbutazone\(^{32}\) and the antibacterial activity was comparable to penicillin and streptomycin on gram-positive and gram-negative organisms\(^{33}\).

Kelm et al. reported antioxidant bioassay of Ocimum sanctum yielded cirsilineol, cirsimaritin, isothymusin, isothymonin, apigenin, rosmarinic acid and eugenol and also observed potent anti-inflammatory (COX-I & II inhibitory) activity\(^{34}\). Ocimum sanctum possesses antimicrobial and anti-inflammatory activities\(^{35,36}\). Ocimum sanctum was found to possess significant anti-inflammatory activity against PGE2, LT and arachidonic acid, and the results suggested that linolenic acid present in Ocimum sanctum has the capacity to block both the CO and LO pathways of arachidonate metabolism\(^{37}\). Singh et al. observed significant inhibition of leucocyte migration, which suggests that the Ocimum sanctum inhibits enhancement of the vascular permeability and leucocyte migration following inflammatory stimulus\(^{38}\). Godhwani et al. documented that Ocimum sanctum caused an immunostimulation of humoral immunologic response (an increase in antibody titre), as well as of the cellular immunologic response\(^{39}\) and decrease in histamine release from mast cells (humoral immune responses) and in leucocyte migration inhibition (cell-mediated immune responses). This immunomodulatory effect was postulated as mediated by GABAergic pathways\(^{40}\). Orientin and vicenin (isolated from Ocimum sanctum) have strong antioxidant activity\(^{41}\).

The extract from Carum copticum has been documented for potent antibacterial activity against common pathogenic bacteria (Salmonella, Micrococcus and Escherichia coli)\(^{17,42}\). Terminalia belerica was reported for its retroviral reverse transcriptase inhibitory activity\(^{43}\). Another study observed potent antibacterial properties of Terminalia belerica in a formulation with Mel despumatum\(^{44-47}\). Rosa damascena is known for its soothing effect and is also found to be beneficial in conjunctivitis\(^{48}\). Cinnamomum camphora has antibacterial activity against several gram-positive and gram-negative bacteria Mel despumatum has been recommended as an effective remedy in conjunctivitis for preventing infection. Meldespumatum is easily absorbed into the tissues and was found helpful in preserving healthy cornea, enucleated within 6 hours after death. Meldespumatum inhibits the growth of Escherichia coli, Hemophilus influenzae, Proteus, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes, Salmonella species and Vibrio cholerae\(^{49}\).
Therefore, Ophthacare eye drops are clinically beneficial in the management of acute and chronic conjunctivitis by the synergistic (anti-inflammatory, antimicrobial, antioxidant, immunostimulatory and antiallergic) actions of its ingredients.

CONCLUSION
This clinical trial observed a remarkably rapid symptomatic relief and significant reduction in the mean scores for conjunctivitis, congestion, papillae and follicle in the patients with acute and chronic conjunctivitis, without any clinically significant adverse events. Therefore it may be concluded that Ophthacare eye drops are clinically efficient and safe in the management of acute and chronic conjunctivitis.

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