Original Article

Comparative study of the ocular efficacy and safety of diclofenac sodium (0.1%) ophthalmic solution with that of ketorolac tromethamine (0.5%) ophthalmic solution in patients with acute seasonal allergic conjunctivitis

Navdeep Dehar, Anita Gupta[1], Gursatinder Singh[2]

Departments of Pharmacology, M.M.Institute of Medical Sciences and Research, Mullana Ambala, Haryana, [1]Pharmacology, [2]Ophthalmology, Govt. Medical College, Patiala, Punjab, India

Abstract

Background: Seasonal allergic conjunctivitis (SAC) is the most common and most prevalent of allergic disorders which afflict the ocular surface. Of the several treatments available, ophthalmic non-steroidal anti-inflammatory drugs, are generally very safe and tolerable. **Aim:** The aim of this study is to compare the ocular efficacy and safety of diclofenac sodium (0.1%) ophthalmic solution with that of ketorolac tromethamine (0.5%) ophthalmic solution in patients with acute SAC. **Materials and Methods:** Sixty patients with signs and symptoms of SAC were evaluated in an open, randomized, parallel group study. The principle symptoms (ocular itching, burning, discharge, photophobia) and signs (ocular inflammation, lid edema, chemosis, conjunctival mucous, keratitis) were evaluated. **Study Design:** Patients were randomized into two groups of 30 each. Patients in group A received one drop of diclofenac sodium 0.1% and patients in group B received ketorolac tromethamine 0.5% in both the eyes four times a day for fourteen days. Evaluations were performed at day 0, 3, 7 and 14 of the therapy. At each visit, the signs and symptoms were rated using a scale from 0-3 (mild-1, moderate-2 and severe-3). **Results:** Significant clinical and statistical reductions in signs and symptoms from baseline were observed in both groups. Diclofenac sodium 0.1% was superior to ketorolac tromethamine 0.5% in reducing ocular itching ($P < 0.05$) and ocular inflammation ($P < 0.05$), at the final examination. **Conclusion:** Diclofenac sodium showed statistically significant better results at day 3 and 7 compared to ketorolac.

Key words: Allergic conjunctivitis; diclofenac sodium ophthalmic solution; ketorolac tromethamine ophthalmic solution

Introduction

Allergy or hypersensitivity is a state whereby tissues react by an abnormal and injurious response to foreign substances.[1] Conjunctiva is a frequent site of such reactions, and their manifestations are often dramatic in their intensity.[2] Seasonal Allergic Conjunctivitis (SAC) is the most common and most prevalent of allergic disorders which afflict the ocular surface.[3,4] Susceptible individuals typically have a family or personal history of environmental allergies, asthma, bronchitis, food allergies or eczema.[4] Such atopic persons when exposed to airborne allergens, sometimes show debilitating ocular symptoms such as itching, tearing, photophobia or discharge. Chemosis, conjunctival injection and swelling of eyelids commonly occur in association with these symptoms. These signs and symptoms are a result of the actions of chemical mediators released in a cascade of response following exposure to an offending allergen. SAC is classical type I anaphylactic hypersensitivity reaction.[5] Mast cell degranulation is thought to be the initiating step in this process, with release of both preformed and newly formed mediators from the mast cell, including histamine, eosinophil chemotactic factor (ECF), prostaglandins, leukotrienes, etc.

Address for correspondence: Dr. Navdeep Dehar,
Department of Pharmacology, MM Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India
E-mail: nav_dehar@yahoo.com

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Recruitment of other cellular elements of the immune system with release of other mediators occurs secondarily.[6-8]

Allergy has a great impact on society, influencing many quality of life (QOL) parameters.[9] Patients of SAC experience QOL reductions in general health and specific aspects of vision, and also suffer from economic consequences as a result of the disease.[3,10] The loss of productivity contributes to the economic burden of the disease in the same manner as the shared costs of the treatments.[3] The direct and indirect expenditure related to ocular allergy prescriptions have risen from $6 million in 1990s to more than $300 million in the new millennium.[11] Treatment of acute SAC may include systemic medications (antihistamines, mast cell stabilizing agents or corticosteroids), immunotherapy or desensitization injections, as well as topical ocular medications. Topical decongestants, antihistamine agents, mast cell stabilizing agents, corticosteroids or nonsteroidal anti-inflammatory agents have all been used with variable results in the treatment of acute SAC.[12-18] More recently, dual action ophthalmic drugs like olopatadine with both antihistaminic and mast cell stabilizing activity have been used.[19] Multi-action therapies like ketotifen which inhibit eosinophil activation in addition to functioning as an anti-histaminic with mast cell stabilization are useful.[20,21]

Several topical non-steroidal anti-inflammatory drugs (NSAIDs) are currently approved by the Food and Drug Administration (FDA) for human use. Further, only ketorolac tromethamine (0.5%) ophthalmic solution has been approved for the relief of ocular itching due to seasonal allergic conjunctivitis. Diclofenac sodium (0.1%) ophthalmic solution is approved for the relief of ocular inflammation following cataract surgery; and, flurbiprofen sodium (0.03%) is approved for maintenance of pupillary mydriasis during cataract surgery. NSAIDs have also been shown as efficacious in the relief of pain following refractive surgeries, including radial keratotomy and excimer laser photo refractive keratectomy.[22,23] Diclofenac sodium (0.1%) ophthalmic solution has recently been approved for the treatment of photophobia, following incisional refractive surgery. Using a formulation similar to diclofenac ophthalmic solution, several reports found ophthalmic diclofenac to be comparable in effectiveness to dexamethasone, in reducing the ocular signs and symptoms of chronic allergic conjunctivitis.[24] Topical administration of diclofenac sodium 0.1% ophthalmic solution was also found to be more effective than placebo in relieving ocular signs and symptoms of acute SAC.[25]

Due to their ability to potently inhibit prostaglandin synthetase and inhibit inflammatory changes, NSAIDs may be an effective and practical choice for treating allergic conjunctivitis after its onset.[16-18,26,27] The purpose of the present study was to compare the safety and efficacy of diclofenac sodium (0.1%) ophthalmic solution with ketorolac tromethamine (0.5%) ophthalmic solution in relieving the signs and symptoms associated with acute SAC.

Materials and Methods

A prospective, randomized, open, parallel group, two weeks comparison study was performed in 60 patients with clinically diagnosed acute SAC. The study was conducted from November 2005 to June 2007 at the Outpatient Department (OPD) of Ophthalmology of a tertiary care hospital in North India. The Institutional Ethics Committee approved the clinical protocol and patients gave their informed written consent prior to participation in the trial. A detailed history and physical examination was carried out. Clinical diagnosis was established by the presence of bilateral symptoms, clinical history of the patient, presence of a positive skin test to a current seasonal allergen, slit lamp examination and using a standardized descriptive scale: a grade of 3+ itching in at least one eye, or a grade of 3+ bulbar conjunctival infection in at least one eye. As patients enrolled in the trial, they were assigned a number in sequence, according to a computer generated randomization schedule. Patients with marked bilateral ocular itching and history of seasonal allergic conjunctivitis confirmed by a positive skin test to appropriate pollen were included in the study.

Patients having an active ocular disease or infections, history of ocular surgery, serious medical illness, allergy to aspirin or other non-steroidal anti-inflammatory drugs, and patients on concurrent treatment for other allergic signs and symptoms like rhinitis were excluded from the study. If the patients were using corticosteroids or NSAIDs, their use was discontinued for at least two weeks prior to the initiation of the therapy. Any antihistaminic drug being used was discontinued at least seventy two hours prior to entering the study. Patients were randomized into 2 groups of 30 each: Group A patients were assigned to receive one drop each of diclofenac sodium 0.1% and Group B were assigned to receive one drop each of ketorolac tromethamine 0.5% in both the eyes four times a day for seven days. Evaluations were performed at baseline (day 0), mid-week (day 3), day 7 and day 14 after the initiation of the therapy. At each visit, the signs and symptoms were rated by the physician using a scale from 0-3(mild-1, moderate-2, severe-3) [Table 1]. Medication compliance was queried and recorded. Benefits of the medication were assessed by slit lamp, and both the physician and the patient assessed the overall therapeutic response of each eye using a scale from 0-2 (no improvement – 0, improved – 1, much improved – 2).

Data were collected for both the eyes. The analysis of each variable was performed on the change from baseline values,

using two tailed student '*t*' test. A '*P*' value less than or equal to 0.05 was considered statistically significant. In addition, the demographic variables were analyzed using Pearson's chi-square test. At each visit, patients were enquired about any complaints that might have indicated an adverse drug reaction such as hyperemia, burning/ stinging, blurred vision, corneal ulceration and keratitis. Any such adverse reaction reported was recorded and analyzed.

Results

Sixty patients (42 males and 18 females) with mean age of 10.26 ± 3.86 years (range 4-18 years) with clinically diagnosed acute SAC were enrolled in the study and evaluated for efficacy and safety of both the drugs. Differences in demographic characteristics and medical histories were statistically non-significant between the two groups ($P > 0.05$) [Table 2]. No serious adverse events were reported during the study. Minor adverse reaction included initial burning and stinging on instillation of medication (Group A 6.67%, Group B 10%). However, this did not indicate the discontinuation of the therapy. With diclofenac treatment, the mean scores for all the signs and symptoms were significantly one grade lower at midweek and at the end of the study than baseline values (except for conjunctival mucous and keratitis). Mean values for itching decreased from 3.0 at baseline to 1.16 at the end of study. Evaluation of other ocular symptoms (e.g., burning / stinging, discharge / tearing, photophobia, foreign body sensation and swollen eye) at mid-week and at the study end showed lower mean values in diclofenac group than the ketorolac treated eyes [Table 3 and Figure 1]. For conjunctival inflammation, there was a significant treatment response favoring diclofenac over ketorolac at mid-week ($P < 0.001$) and study end ($P < 0.001$). The signs of lid oedema and conjunctival chemosis did not show much improvement after day, 3 and the values remained the same till the study end for both the groups. However, conjunctival mucous and keratitis did not show any improvement at all with any of the therapies [Table 4, Figure 2]. An evaluation of the therapeutic response at the completion of the treatment revealed that the number of patients reporting no change in signs and symptoms were more in ketorolac treated groups [Table 5].

Discussion

Acute SAC is a condition accounting for 50% of the ocular allergies. India is one of the tropical countries where extremes of temperature during the summer make the condition worse; and, increased exposure to pollens and environmental pollutants add to the disease process. Because of the impact on the quality of life experienced by the patients of SAC, we were interested in studying if diclofenac alleviated the allergic symptoms better than ketorolac. While numerous treatment options exist, each choice is limited by potential side effects. Topical decongestants, usually naphazoline, tetrahydrozoline or oxymetazoline are perceived as irritating by many patients, producing or increasing lacrimation and a burning sensation. These agents can produce reactive hyperemia on withdrawal,

Table 1: Symptoms and signs of allergic conjunctivitis evaluated in the study[16,17]

Symptoms/signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Itching	Occasionally feel like rubbing	Occasionally rubbing eye	Rubbing eye daily
Burning/stinging	Occasional	Daily with occasionally closing	Close eye daily
Discharge/tearing	Occasionally wipe eye	Wipe eye daily	Wipe eye several times daily
Photophobia	Occasional	Daily and occasional squint eye	Occasionally close eye
Foreign body sensation	Occasionally feels sandy	Feels sandy daily	Occasionally look for foreign body
Swollen eyes	Lid feels full in morning	Lid feels full all day	Interpalpebral fissure decreased
Conjunctival chemosis	Minimal chemosis	Focal areas of chemosis	Obvious chemosis
Conjunctival injection/ inflammation	Minimal redness	Obvious but not diffuse redness	Diffuse redness
Conjunctival mucus	No mucous strands	Few mucous strands	Easily detectable mucous strands
Keratitis	Mild	Moderate	Severe

Table 2: Pre trial, pretreatment patient characteristics: Group comparisons – Demographics in the study

Variable		Group A (n = 30) (%)	Group B (n = 30) (%)	'P' value
Age	Range	4-18 yrs	4-18 yrs	0.765
	Mean ± SD	10.26 ± 3.86	10.56 ± 3.88	
Sex	Male	20 (66.67)	22 (73.33)	0.573
	Female	10 (33.33)	8 (26.67)	
Habitat	Rural	23 (76.67)	26 (86.67)	0.317
	Urban	7 (23.33)	4 (13.33)	
Duration of disease	Range	5 mths-6 yrs	5 mths-10 yrs	0.459
	Mean ± SD	2.14 ± 1.75	2.58 ± 6.26	

SD = Standard deviation

Table 3: Summary of overall evaluation: Mean scores (symptoms) as seen in the study

Symptoms#	Baseline	Day 3	'P' value+	Day 7	'P' value+	Day 14	'P' value+
Ocular itching							
Diclofenac	3.0	1.46	< 0.001	1.20	< 0.001	1.16	< 0.001
Ketorolac	3.0	1.73	< 0.001	1.53	< 0.001	1.46	< 0.001
'P' value *		0.035		0.018		0.029	
Burning/stinging							
Diclofenac	2.10	1.16	< 0.001	1.03	0.0003	1.0	0.147
Ketorolac	2.06	1.26	< 0.001	1.20	0.043	1.1	0.016
'P' value*		0.455		0.028		0.018	
Discharge/tearing							
Diclofenac	2.13	1.30	< 0.001	0.90	< 0.001	0.86	< 0.001
Ketorolac	2.16	1.43	< 0.001	1.13	< 0.001	1.06	< 0.001
'P' value*		0.050		0.006		0.005	
Photophobia							
Diclofenac	1.66	0.73	< 0.001	0.50	< 0.001	0.46	< 0.001
Ketorolac	1.66	0.93	< 0.001	0.83	< 0.001	0.80	< 0.001
'P' value*		0.090		0.002		0.007	
Foreign body sensation							
Diclofenac	1.66	0.96	< 0.001	0.60	< 0.001	0.50	< 0.001
Ketorolac	1.70	1.03	< 0.001	0.90	< 0.001	0.86	< 0.001
'P' value*		0.624		0.021		0.004	
Swollen eye							
Diclofenac	1.36	0.83	< 0.001	0.90	< 0.001	0.86	< 0.001
Ketorolac	1.36	1.06	0.001	1.00	< 0.001	0.96	< 0.001
'P' value*		0.034		0.371		0.530	

*Between group comparison (unpaired student't' test); +With in group comparison (paired student 't' test); #Scale: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe

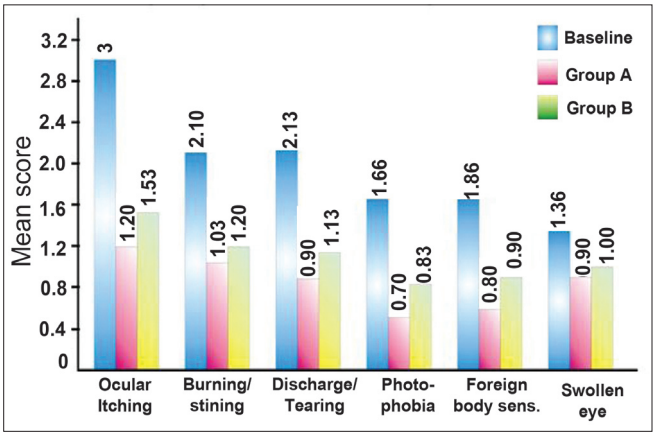

Figure 1: Symptom evaluation at day 7 in the study

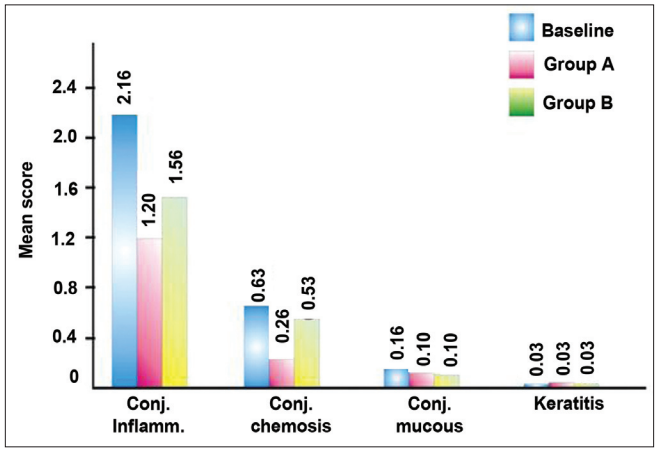

Figure 2: Sign evaluation at day 7 in the study

may precipitate angle closure glaucoma and may produce punctate keratitis. Overuse has been reported to cause headaches, dizziness, nervousness eyestrain, and, on rare occasions, cardiac arrhythmia.[28] Topical antihistaminics are generally well tolerated; however, may produce burning and/or stinging on instillation in a significant percentage of patients. Contact hypersensitivity reactions to topical antihistaminics are not rare,[28] and persistent or increased ocular redness is experienced by some patients. Topical mast cell stabilizing agents are generally well tolerated; however, can produce burning and/or stinging on instillation in as many as 15% of patients. Other side effects include keratitis sicca, ocular irritation with increased lacrimation, ocular itching or blurred vision. These drugs may also require several weeks before therapeutic effects are apparent and this is consistent with their presumed mechanism of action.[12,13,15] The side effects of topical corticosteroids are well known. While the efficacy of these agents for the treatment of allergic disease is excellent, serious limitations to their chronic use include: elevation of intraocular pressure, accelerated development of cataract, decreased resistance to infection, mydriasis, delayed corneal wound healing, ptosis and optic atrophy.[29]

Topical NSAIDs are generally safe and well tolerated, producing few ocular side effects. Burning and/or stinging on instillation

Table 4: Summary of overall evaluation: Mean scores (signs) seen in the study

Signs#	Baseline	Day 3	'P' value+	Day 7	'P' value+	Day 14	'P' value+
Conjunctival inflammation							
Diclofenac	2.16	1.50	< 0.001	1.20	< 0.001	1.16	< 0.001
Ketorolac	2.16	1.83	0.030	1.56	< 0.001	1.53	< 0.001
'P' value*		0.039		0.032		0.030	
Lid edema							
Diclofenac	0.26	0.16	0.083	0.16	0.083	0.16	0.083
Ketorolac	0.23	0.20	0.326	0.20	0.326	0.20	0.326
'P' value*		0.744		0.744		0.744	
Conjunctival chemosis							
Diclofenac	0.63	0.56	0.161	0.26	0.001	0.23	0.001
Ketorolac	0.63	0.56	0.161	0.53	0.083	0.53	0.083
'P' value*		1.000		0.035		0.016	
Conjunctival mucous							
Diclofenac	0.16	0.13	0.326	0.10	0.161	0.10	0.161
Ketorolac	0.16	0.13	0.326	0.10	0.161	0.10	0.161
'P' value*		1.000		1.000		1.000	
Keratitis							
Diclofenac	0.03	0.03	-	0.03	-	0.03	-
Ketorolac	0.03	0.03	-	0.03	-	0.03	-
'P' value*		-		-		-	

*Between group comparison (unpaired student't' test); +With in group comparison (paired student 't' test); #Scale: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe

Table 5: Evaluation of the therapeutic response at the end of study

Symptoms/Signs	Much improved (%)	Improved (%)	No change (%)	Worse
Ocular itching				
Diclofenac	24 (80)	6 (20)	0	0
Ketorolac	15 (50)	15 (50)	0	0
Burning/Stinging				
Diclofenac	13 (43.33)	14 (46.66)	3 (10)	0
Ketorolac	5 (16.67)	18 (60)	7 (23.33)	0
Discharge/Tearing				
Diclofenac	17 (56.66)	13 (43.33)	0	0
Ketorolac	15 (50)	9 (30)	6 (20)	0
Photophobia				
Diclofenac	20 (66.67)	8 (26.67)	2 (6.67)	0
Ketorolac	18 (60)	4 (13.33)	8 (26.67)	0
Foreign body sensation				
Diclofenac	7 (23.33)	21 (70)	2 (6.67)	0
Ketorolac	2 (6.67)	21 (70)	7 (23.33)	0
Swollen eye				
Diclofenac	0	15 (50)	15 (50)	0
Ketorolac	0	12 (40)	18 (60)	0
Conjunctival inflammation				
Diclofenac	25 (84)	5 (16)	0	0
Ketorolac	19 (64)	11 (36)	0	0

have been reported by 15% of patients in previous studies; however, drug discontinuation is infrequently required. Other side effects reported include corneal ulceration, delayed epithelial wound healing, punctate keratitis and corneal anesthesia.[30] The results of this study demonstrated that the use of either diclofenac sodium ophthalmic 0.1% solution or ketorolac tromethamine 0.5% ophthalmic solution four times daily produces prompt relief of many of the ocular symptoms of SAC within 3 days and provides continued relief of ocular symptoms for at least 14 days. Both treatments evaluated in this study were well tolerated, with a lower incidence of complaints of burning and stinging following instillation of eye drops than what has been reported previously [10% for group A (diclofenac sodium) and 6.67% for group B (ketorolac tromethamine)]. By far, the most intriguing finding in this study was that relief of both signs and symptoms of SAC occurred as rapidly as 3 days after instillation of a single drop of either NSAIDs employed. The mechanism of such a rapid effect

remains speculative. In the current clinical study, diclofenac sodium 0.1% was clinically and statistically more effective than ketorolac tromethamine 0.5% for the relief of pain or soreness at day 3 and 7. This rapid onset of effect may be independent of effects on prostaglandin synthetase. Additional work will be necessary to elucidate the mechanisms involved in this finding.

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