COMPARATIVE STUDY OF TOPICAL OLOPATADINE HYDROCHLORIDE 0.1% WITH KETOTIFEN FUMARATE 0.025% IN TREATMENT OF ALLERGIC CONJUNCTIVITIS

BY

Dr. DHARMISTHA PATEL, MBBS

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DOCTOR OF MEDICINE
IN
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Under the guidance of

Dr. SARALA. N, MD

DEPARTMENT OF PHARMACOLOGY
SRI DEVARAJ URS MEDICAL COLLEGE, KOLAR

April 2014

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"COMPARATIVE STUDY OF TOPICAL OLOPATADINE HYDROCHLORIDE 0.1% AND KETOTIFEN FUMARATE 0.025% IN TREATMENT OF ALLERGIC CONJUNCTIVITIS"** is a bonafide and genuine research work carried out by me under the direct guidance of **Dr. SARALA. N, M.D** Professor and HOD, Department of Pharmacology Sri Devaraj Urs Medical College, Tamaka, Kolar.

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Dr. DHARMISTHA PATEL

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Date:

Place: Kolar

SIGNATURE OF THE GUIDE

Dr. SARALA. N, MD

PROFESSOR AND HEAD
DEPARTMENT OF PHARMACOLOGY

CERTIFICATE BY THE CO-GUIDE

This is to certify that the dissertation entitled **"COMPARATIVE STUDY OF TOPICAL OLOPATADINE HYDROCHLORIDE 0.1% AND KETOTIFEN FUMARATE 0.025% IN TREATMENT OF ALLERGIC CONJUNCTIVITIS"** is a bonafide research work done by **Dr. DHARMISTHA PATEL** in partial fulfillment of the requirement for the degree of **M.D IN PHARMACOLOGY.**

Date:

Place: Kolar

SIGNATURE OF THE CO-GUIDE

Dr. NARENDRA P DATTI, MD

PROFESSOR AND HEAD
DEPARTMENT OF OPHTHALMOLOGY

ENDORSEMENT BY THE HOD, PRINCIPAL/ HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"COMPARATIVE STUDY OF TOPICAL OLOPATADINE HYDROCHLORIDE 0.1% AND KETOTIFEN FUMARATE 0.025% IN TREATMENT OF ALLERGIC CONJUNCTIVITIS"** is a bonafide research work done by **Dr. DHARMISTHA PATEL** under the guidance of **Dr. SARALA. N, MD** Professor and HOD, Department of Pharmacology.

Dr. SARALA. N	**Dr. M.B. SANIKOP**
SEAL & SIGNATURE OF THE HOD	SEAL & SIGNATURE OF THE PRINCIPAL
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Dr. DHARMISTHA PATEL

SRI DEVARAJ URS MEDICAL COLLEGE, TAMAKA, KOLAR.

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CERTIFICATE

This is to certify that, the ethics committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved the dissertation work of **Dr. DHARMISTHA PATEL**, a postgraduate student in the Department of Pharmacology of Sri Devaraj Urs Medical College entitled "**COMPARATIVE STUDY OF TOPICAL OLOPATADINE HYDROCHLORIDE 0.1% AND KETOTIFEN FUMARATE 0.025% IN TREATMENT OF ALLERGIC CONJUNCTIVITIS"** to be submitted to the Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar.

MEMBER SECRETARY **PRINCIPAL**

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Date:

Signature of the Candidate

Place: Kolar

Dr. DHARMISTHA PATEL

Dedicated with

REVERENCE

to

My Parents

LIST OF ABBREVIATIONS

AC	Allergic conjunctivitis
QOL	Quality of life
IOIS	International Ocular Inflammation Society
SAC	Seasonal allergic conjunctivitis
PAC	Perennial allergic conjunctivitis
AKC	Atopic keratoconjunctivitis
VKC	Vernal keratoconjunctivitis
GPC	Giant papillary conjunctivitis
CDC	Contact dermatoconjunctivitis
CALT	Conjunctiva associated lymphoid tissue
IgE	Immunoglobulin E
IgM	Immunoglobulin M
NSAIDs	Non steroidal anti-inflammatory drugs
Ag	Antigen
MCH	Major histocompatibility complex
Ab	Antibody
T cells	T lymphocytes
B cells	B lymphocytes
Tc	Cytotoxic T cells
T_H2	T helper cells
FC	Crystallisable fragment of immunoglobulin
LC	Langerhans cells
CD4	Cluster of differentiation 4

IL	Interleukins
EPR	Early phase reaction
TNF	Tumor necrosis factor
LPR	Late phase reaction
EMBP	Eosinophil major basic protein
PAF	Platelet activating factor
CPT	Conjunctival provocation test
α1	Alfa 1
H_1 and H_2	Histamine receptors 1 and 2
IOP	Intraocular pressure
NF-κβ	Nuclear factor - kappa beta
IP_3	Inositol trisphosphate
DAG	Diacylglycerol
Ca^{2+}	Calcium
Olopatadine HCl	Olopatadine hydrochloride
NO	Nitric oxide
ICAM	Intracellular adhesion molecules
LDH	Lactate dehydrogenase
GM-CSF	Granulocyte macrophage colony stimulating factor
PCA	Passive cutaneous anaphylaxis
SRS-A	Slow reacting substance of anaphylaxis
T½	Half life
M1	N-monodesmethyl form
ADRs	Adverse drug reactions

ABSTRACT

Background and Objectives

Allergic conjunctivitis (AC) is an atopic ocular disorder associated with itching, redness, tearing, pains, burning sensation and foreign body sensation. These symptoms affect academic performance and the quality of life (QOL) of sufferers resulting in loss of productivity. It is an inflammatory process caused by an immunoglobulin E (IgE) mediated immune or immediate hypersensitivity mechanism resulting from direct contact of the allergen with the conjunctival triggering mast cell activation and the release of different mediators. Topical medications like olopatadine hydrochloride 0.1% and ketotifen fumarate 0.025% have both mast cell stabilizing and antihistaminic properties.

Objectives of this study are:

1. To study the efficacy and safety of Olopatadine HCl 0.1% and Ketotifen fumarate 0.025% in allergic conjunctivitis (AC)
2. To study the cost effectiveness of the above drugs
3. To study the Quality Of Life (QOL) in AC

Materials and methods

This study was conducted on patients presenting to the Department of Ophthalmology, R.L. Jalappa Hospital and Research Centre. Patients clinically diagnosed with AC were randomly divided into two groups of 60 patients each to receive either topical olopatadine HCl 0.1% or ketotifen fumarate 0.025%.

They were followed up on 4th, 15th and 30th day for evaluation of symptoms, signs and QOL scoring. Adverse effects were recorded and cost effectiveness analyzed

Interpretation and Results

120 patients, 67 males and 53 females with mean age of 36.35 ± 11 years. At baseline individual, total AC and QOL scores were comparable. The above scores reduced significantly (p=0.001) by 4th and 15th day compared to baseline in both groups. Between groups by 4th day the itching, tearing, hyperaemia and total AC scores reduced significantly (p=0.001) and by 15th day there was significant reduction (p=0.001) in itching, tearing, papillae and total AC score in patients receiving olopatadine. QOL score was comparable between the groups. Around 10% and 18% reported adverse reactions. The cost of olopatadine HCl per patient was 84 rupees, whereas for ketotifen fumarate it ranged from 57 to 114 rupees.

Conclusion

Olopatadine HCl provided qicker relief of symptoms, improvement in signs and QOL in patients with allergic conjunctivitis with lesser side effects compared to ketotifen fumarate.

Key words: Allergic conjunctivitis, olopatadine hydrochloride and ketotifen fumarate

CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

INTRODUCTION

Allergic conjunctivitis (AC) is an atopic ocular disorder associated with itching, redness, tearing, pains, burning sensation and foreign body sensation.[1,2] These symptoms affect academic performance and the quality of life (QOL) of sufferers resulting in loss of productivity.[3] AC can affect both children and adults, often coexisting with other allergic diseases such as asthma, atopic dermatitis or food allergy.[4] According to the classification of ocular allergy proposed in 2006 by the International Ocular Inflammation Society (IOIS), based on immuno-pathological mechanisms, AC is a type of ocular allergy which is subdivided into seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC). It also includes atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), giant papillary conjunctivitis (GPC) and contact dermato-conjunctivitis (CDC) – which differs in their manifestations, clinical course and treatment.[5]

AC is an inflammatory disorder of the transparent mucous membrane that covers the sclera. It is a self limiting process caused by an immunoglobulin E (IgE)-mediated immune or immediate hypersensitivity mechanism resulting from direct contact of the allergen with the conjunctival surface in sensitized patients – triggering mast cell activation and the release of different mediators.[6] The others include the neurogenic and systemic immune mechanisms.[4]

The treatment of AC aims to prevent or minimize allergen contact with the conjunctiva based on a series of protective and preventive measures (environmental control, cold compresses, eye lubricants without preservatives, contact lenses, etc.) and control the symptoms triggered by the allergic inflammatory process by administering

antihistamines, mast cell stabilizers, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Topical medications like olopatadine hydrochloride (HCl) 1 mg/ml and ketotifen fumarate 250 mg/ml have both mast cell stabilizing and antihistaminic properties. It has been reported that these drugs have good efficacy and safety in treating SAC so they have the advantage as prophylactic agent to prevent mast cell degranulation which brings about symptomatic relief following the onset of symptoms.[7] Since there is paucity of data comparing the efficacy of these two drugs in the treatment of AC in India this study has been undertaken.

AIMS
&
OBJECTIVES

AIMS AND OBJECTIVES

1. To study the efficacy of Olopatadine HCl 0.1% and Ketotifen fumarate 0.025% in allergic conjunctivitis (AC)
2. To study the safety profile of Olopatadine and Ketotifen in AC
3. To study the cost effectiveness of the above drugs
4. To study the Quality Of Life (QOL) in AC

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Conjunctivitis or inflammation of the conjunctiva is commonly referred to as "pink eye" or "red eye".[8] Allergic eye disease is a common ocular atopic disorder. The eye is probably the most common site for the development of allergic inflammatory disorders, because it has no mechanical barriers to prevent impact of allergens on its surface. Allergic conjunctivitis (AC) is associated with ocular discomfort such as itching, redness, tearing, pain, burning sensation and foreign body sensation and has an impact on the quality of life of patients.[9]

ANATOMY [10]

Conjunctiva is a fine, translucent mucous membrane which joins and covers the anterior surface of eyeball and posterior side of the eyelids. The name "conjunctiva" has originated from the term "conjoin" which means "to join".[11] It covers the posterior surface of the lids and reflects to cover the anterior part of the sclera, then becomes continuous with the corneal epithelium. At the lid margin conjunctiva is continuous with the skin.

Parts of conjunctiva: Broadly conjunctiva is divided into palpebral conjunctiva, fornices and bulbar conjunctiva Fig.1.[12]

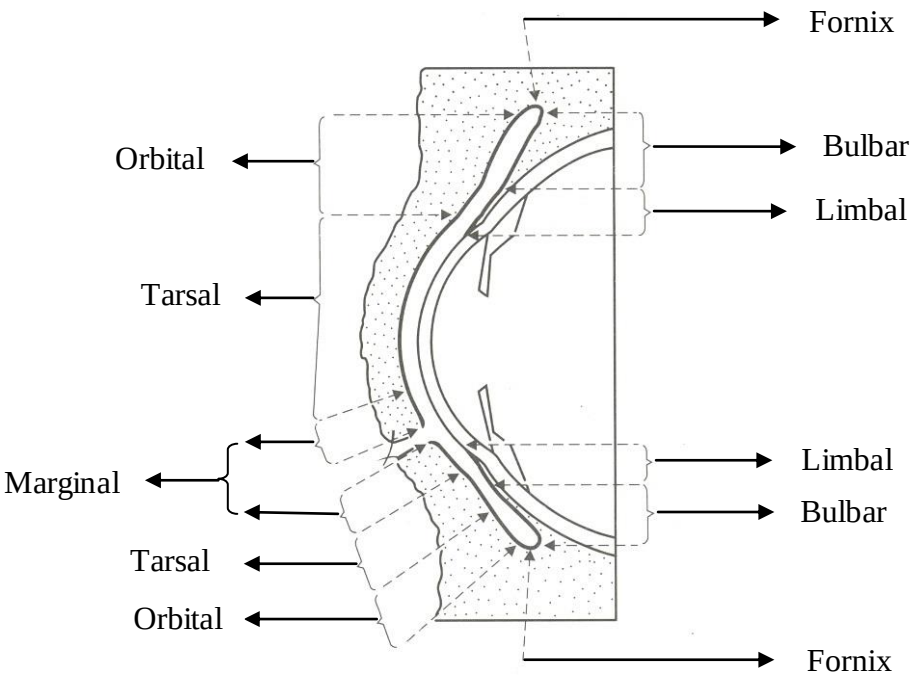


Fig. 1- Parts of conjunctiva

Palpebral conjunctiva: It is the part of the conjunctiva which lines the under surface or posterior surface of the eyelid. Palpebral in Latin means "an eyelid".

- Marginal conjunctiva is a transitional zone between the skin of the eyelid and conjunctiva proper. It starts from the intermarginal strips of the eyelid as a continuation of the skin and is made up of stratified epithelium. It continues to the back or posterior surface of the lid for a distance of 2 mm, up to a shallow groove or fold called sub tarsal sulcus or sulcus subtarsalis, where it merges with the conjunctiva proper. This groove is a common site of foreign body lodgment. Here perforating branches of marginal arcade pierce the tarsal plate to supply the conjunctiva.
- Tarsal conjunctiva is a very vascular and adherent to the tarsal plates. Adherence is less marked in lower than the upper eye lid where it is fully adhered to the

whole tarsal plate. Tarsal glands are visible through the transparent tarsal conjunctiva as yellow line running parallel to each other in a vertical direction.

- Orbital conjunctiva is a loose covering between the tarsal plate and fornix. It is thrown in to horizontal folds during eye movements. In upper eyelid it lies over the Muller's muscle.

Bulbar conjunctiva: It is the thinnest of the all the parts of conjunctiva and so transparent that underlying white sclera and vessels are seen clearly. It is loosely attached except for a zone of 3mm near the limbus and near insertions of the recti muscles.

In limbus, conjunctiva, tenon's capsule and sclera fuse together. Limbal conjunctiva is the part of the bulbar conjunctiva which covers the limbal region and fuses with the corneal epithelium.

Conjunctiva of the Fornix: It is fold lining the cul-de-sac formed by conjunctiva covering the posterior surface of the lids to the conjunctiva covering the anterior surface of the globe. The conjunctiva here is comparatively thicker and loosely attached in order to allow free movement of the globe. It is divided into 4 regions:

- Superior fornix lies between upper lid and the globe and extends 8 to 10 mm from the upper border of the limbus.
- Inferior fornix lies between lower lid and the globe and extends up to 8 mm below the lower part of limbus.
- Lateral fornix lies between the lateral canthus and the globe and extends for 15 mm from the lateral part of the limbus.
- Medial fornix is the shallowest and contains caruncle and the plica semilunaris.

HISTOLOGY [13]

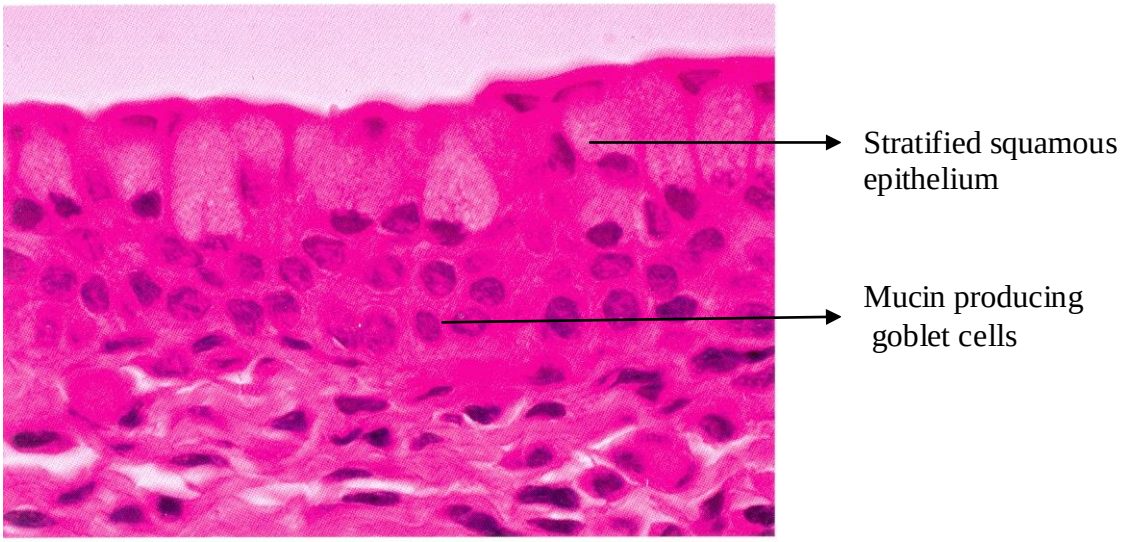


Fig. 2 - Parts of conjunctiva

Microscopically conjunctiva consists of three layers:

1. The **epithelium** is non- keratinizing and around five layers deep. Goblet cells are round and oval with 10-20 µm in size. They are seen throughout the conjunctiva lying in between the cells of conjunctival epithelium and secret mucin. They arise from basal layer of epithelium, gradually enlarge, become larger as they reach the surface of the conjunctiva, discharge their mucin content and finally shed away (Fig. 2).[14]
2. The **stroma** (substantia propria) consists of richly vascularised loose connective tissue. The adenoid superficial layer does not develop until about three months after birth. The deep fibrous layer merges with the tarsal plates. The accessory lacrimal glands of Krause and Wolfring are located deep within the stroma. Mucus from the goblet cells and the secretions from the accessory lacrimal glands are essential components of the tear film. Numerous mast cells, lymphocytes, plasma cells and neutrophils are normally present in this layer. The conjunctiva contains high number

of mast cells in substantia propria.[15] The total number of mast cells in the conjunctiva and adnexal tissue will be around 50 million.[9] Allergic conjunctivitis is an immediate type (Type I) allergic response mediated by IgE.[16] In patients with allergic conjunctivitis the mast cells have been found in conjunctival epithelium also.

Conjunctiva associated lymphoid tissue (CALT) is responsible for the initiation and regulation of ocular surface immune responses.[13] It consists of lymphocytes within the epithelial layers, lymphatics and associated blood vessels, with a diffuse stromal component of lymphocytes and plasma cells, including follicular aggregates.

BLOOD SUPPLY [17]

Arteries

The conjunctival arteries are derived from two sources:

1. The palpebral branches of the nasal and lacrimal arteries of the lids.
2. The anterior ciliary artery.
3. The post tarsal plexus of the lid which is formed by the marginal and peripheral

artery of the upper lid supplies the palpebral conjunctiva. The perforating vessels from the peripheral palpebral arcade supply most of the fornical conjunctiva. This arcade sends descending branches to supply the tarsal conjunctiva and also anastomoses with vessels from the marginal arcade and ascending branches which pass into the superior and inferior fornix to continue around the fornices to the bulbar conjunctiva as the posterior conjunctival artery.

The anterior ciliary arteries give off anterior conjunctival arteries just before piercing the globe. These arteries send branches to the pericorneal plexus and the bulbar

conjunctiva of the limbal area. Here there is free anastomosis in the subconjunctival and episcleral tissues between the anterior conjunctival vessels and the terminal branches of the posterior conjunctival vessels resulting in zone of palisades of Busaca; thus, there is a close connection between the superficial and the deep vascular system in the limbal area.

Veins

The conjunctival veins are more numerous than arteries. The major part of the drainage from the tarsal conjunctiva and the bulbar conjunctiva is to the palpebral veins. Few tarsal veins empty directly into the superior and inferior ophthalmic veins. Small vessels of the bulbar conjunctiva have anterior venous communications but these are not true anastomoses as it has no muscular walls.

LYMPHATICS [17]

The conjunctiva has lymphatics arranged in the following plexus:

1. Superior plexus consisting of small vessels placed below the capillaries.
2. Deeper plexus of larger vessels in the fibrous portion of the substantia propria. These are important in the mediation of immunological reaction that occurs in certain ocular diseases and surgical conditions.
3. The superficial plexus drains the limbal area. These are larger channels running circumferentially 7 to 8mm behind the limbus to form an incomplete pericorneal lymphatic ring.

The recurrent nasal group and the descending temporal group drain at medial canthus and large connecting vessels from the inferior fornix at lateral canthus. Laterally placed

vessels flow to the periauricular lymph nodes and medially placed into the submaxillary lymph nodes.

NERVE SUPPLY [17]

The conjunctiva is supplied by the first division of the trigeminal nerve. The nerves are infratrochlear branch of the nasociliary nerve, lacrimal nerve and infraorbital nerve from the maxillary division of the trigeminal nerve. The limbal area is supplied by the branches from the ciliary nerves. All nerves form a network on the conjunctiva and terminate either peripherally in various form of specialized endings or on blood vessels and epithelial cells. The majority of the nerve endings are free non-myelinated nerve endings.

EPIDEMIOLOGY [9]

It has been reported that about one-fifth of the entire human population suffers one form of allergy or another of which about 20% is due to allergic conjunctivitis.[7,18,19] The prevalence of allergic conjunctivitis varies worldwide, usually ranging between 15% to 40%.[20] These variations may be attributed both to genetic and non genetic factors.

Genetics also play a role in the predisposition to allergic diseases. Although the specific type of allergy expressed by the individuals may differ within the family, the incidence of allergic disorders is approximately three times higher in the atopic families than in non-atopic families. Children who have both maternal and paternal family history of atopy manifest allergy before puberty and risk is more than 50% and doubled in children who have one parent with history of atopy. Several genes are suspected to be

associated with atopy, such as 5q31-33. Children do not inherit the allergic disorder per se, but instead an 'allergic predisposition' that can be contributed equally by both the parents, suggesting that this is an autosomally carried trait.

The non genetic risk factors include environmental allergens such as pollens from trees, grasses and weeds of which ragweed has been identified as the most common cause of conjunctivitis in United States. Animal dander and house dust mites, moulds, air pollution and some food substances like groundnuts and pineapple also trigger allergic conjunctivitis.[1]

ETIOPATHOGENESIS

The term allergy was coined by Clemens von Pirquet in 1906 to describe an altered reaction of the immune system to the foreign bodies, irrespective of whether it resulted in immunity or a harmful effect.[21] Today it is restricted to situation where an exaggerated sensitivity (hypersensitivity) results from a heightened or altered reactivity of the immune system in response to foreign substances.

The Immune System [22]

The body is able to defend itself from potentially harmful infectious (bacteria, viruses and other pathogens) and non infectious agents and at times, normal host tissues itself becomes subjected to inappropriate immune attack, such as in autoimmune diseases. Skin and barrier tissues form the first line of defense, once an offending agent penetrates these barriers, there will be innate and adaptive responses by the immune system. This system is composed of specialized effector cells that sense and respond to foreign antigens (Ag) and other molecular patterns. The cells of the immune system are derived

from myeloid stem cells and lymphoid stem cells. Myeloid stem cells give rise to precursors of cells of the innate immune system, whereas lymphoid stem cells generate precursors of cells of the adaptive immune system.

Innate Immunity

Cells of the innate immune system are the first responders to an offending agent that has penetrated the skin or another barrier. Innate immune cells perform three important tasks.

1. These cells defend against bacterial and parasitic infections, either by neutralizing the infectious agent with secreted cytotoxic proteins or by phagocytosis of the bacterium or parasite.
2. Phagocytosis of the offending agent initiates proteolytic digestion of microbial macromolecules to fragments (antigens) that are then displayed, together with major histocompatibility complex (MHC) class II proteins, on the surface of antigen- presenting cells. In turn, these antigen-presenting cells, which include macrophages and dendritic cells activate cells of the adaptive immune system.
3. The innate immune cells secrete numerous cytokines that further amplify the immune response. The major cell types of the innate immune system include granulocytes (neutrophils, eosinophils and basophils), mast cells and antigen-presenting cells (macrophages and dendritic cells).

Macrophages derived from the monocytes are involved in the chronic inflammation. They phagocytose cellular and the foreign debris. Dendritic cell transports and presents the antigen to T cells. Both the macrophages and the dendritic cell function as the antigen presenting cell. Neutrophils phagocytosis and kills the invading pathogens. Eosinophils

defend against the parasites and basophils/ mast cell release histamine, leukotrines and other mediators after exposure to antigen.

Adaptive Immunity

Characteristics include:

1. Ability to respond to a variety of antigen in specific manner.
2. Discriminate between foreign antigens and self antigens of the host.
3. Respond to a previously encountered antigen in a learned way by initiating a vigorous memory response.

This adaptive response helps in the production of antibodies (Ab), which are the effectors of humoral immunity and the activation of T lymphocytes/ cytotoxic T cells (T_C) which are the effectors of cell mediated immunity. The B cells synthesizes and secrets antibody.

Hypersensitivity [23]

Can be classified as antibody mediated (Type I, II and III) or cell mediated (Type IV) according to Gell and Coombs classification.[24]

Type I: Immediate Hypersensitivity

- Results from cross-linking of membrane-bound IgE on blood basophils or tissue mast cells by antigen.
- Cross-linking causes cells to degranulate, releasing substances such as histamine, leukotrienes and eosinophil chemotactic factor.
- Bronchial asthma, systemic anaphylaxis (from insect envenomation, ingestion of certain foods, or drug hypersensitivity).

Type II: Cytotoxic Antibody mediated (IgG, IgM)

- Results from the formation of antigen-antibody complexes between foreign

antigen and IgM or IgG immunoglobulins.

- Blood transfusion reaction, hemolytic disease of the newborn.

Type III: Immune Complex mediated

- Presence of elevated levels of antigen-antibody complexes.
- Deposition of these complexes on basement membranes leading to activation of complement system to produce components with anaphylatoxic and chemotactic activities (C5a, C3a, C4a) that increase vascular permeability and recruit neutrophils to the site of complex deposition.
- Glomerulonephritis, serum sickness.

Type IV: Delayed Hypersensitivity

- Occur 2–3 days after exposure to the sensitizing antigen.
- Induces a local inflammatory response and causes tissue damage characterized by the influx of antigen-nonspecific inflammatory cells, especially macrophages and neutrophils leading to tissue damage.
- Graft versus host reaction.

Immunological mechanisms of allergic conjunctivitis [25]

The eye is the most important target organ of the IgE/ mast cell mediated hypersensitivity reactions. AC is due to the direct exposure of the ocular mucosal surfaces to environmental allergens. Two stages have been defined in AC immune pathophysiology:

1. Sensitization phase reaction that is initiated by preferential activation and polarization of the immune response to environmental antigens and culminates with a generation of a predominant T helper (TH2) immune response and production of IgE antibodies.

3. Effector phase reaction that is initiated with a second encounter with antigen leading to activation of effector mechanisms, such as degranulation of granulocytes and release of histamine.

Sensitization phase reaction

In a localized allergic reaction, an allergen (antigen) first penetrates an epithelial surface (skin, nasal mucosa). With the aid of T helper (TH) cells, the allergen stimulates B lymphocytes to produce IgE antibodies that are specific for that allergen. The IgE then binds to Fc receptors on mast cells and basophils, in a process known as sensitization. Once these immune cells are "sensitized" with IgE antibodies, they are able to detect and respond rapidly to a subsequent exposure to the allergen. Upon such an exposure the allergen binds to and cross-links the IgE/Fc receptor complexes, triggering cell degranulation.

The ocular mucosa has the ability to capture Ag through Langerhans cells (LC) which can process and present Ag to class II MHC molecules and stimulate specific CD4 T cells to induce secretion of interleukin (IL)-4, IL-13 and expression of CD154; this process stimulates B cell proliferation and antibody secreting plasma cells leading to production of IgE antibodies. It has been reported that IgE can be detectable in human tears and B cells located in the conjunctival lymphoid follicles are CD23, CD21 and CD40 suggesting that they might be precursors of IgE producing B cells and contribute to local IgE synthesis.[26, 27]

Effector phase reaction

Allergen induced cell degranulation is the key event in allergic inflammation and leads to early phase symptoms. The allergic cascade begins when antigen binds and crosslinks with two immunoglobulin IgE receptors located on the surface of the conjunctival mast cells. Early phase reaction (EPR) is initiated with a second encounter with the antigen when it binds and cross-links with two immunoglobulin IgE receptors located on the surface of the conjunctival mast cells. The allergen IgE antibody mast cell complex results in the activation of a serine esterase, initiating a change in the Fc portion of the IgE molecule, which is attached to the mast cell membrane. These events lead to an intracellular biochemical cascade resulting in:

- release of preformed mediators such as histamine, proteases and chemotactic factors
- activation of transcription factors and cytokine gene expression and
- production of prostaglandins and leukotrienes by phospholipase A_2 pathway.

Activation of mast cells by IgE in conjunctiva is relevant since it is well known that there are up to 50 million mast cells in ocular and adnexal tissues of human eye and mast cell density is increased in acute and chronic conjunctivitis patients.[9, 28] These activated cells result in the release of certain chemicals such as histamine, serotonin, proteoglycans, serine protease, leukotriene C4 and heparin, that will further bind with their receptors present in other cells (e.g. histamine receptors) and lead to inflammation, irritation, redness and other allergic symptoms. Activated mast cells release several cytokines such as IL-4, IL-6, IL-13, and Tumor Necrosis Factor (TNFα) contributing to increase in local inflammatory response.

Cellular infiltration is the main feature of the late phase reaction (LPR) which begins 4-24 hours after EPR and involves the infiltration of basophils, neutrophils, T lympocytes and mainly eosinophils. Once initiated, LPR can proceed in the presence of little or no detectable allergen-specific IgE antibody.

Mediators have been categorized into three different groups based on their mode of action. Firstly, histamine and the prostaglandins which mediate their action by binding to a specific cell membrane receptor. The second group comprises substances of cell or plasma origin that directly damage tissues, including eosinophil major basic protein (EMBP) and complement. The third consists of chemotactic factors that attract eosinophils and macrophages to the inflammatory site and includes the arachadonic acid metabolites.

PRIMARY MEDIATORS

Histamine

Histamine is an essential mediator of immune and inflammatory responses. It plays a prominent role in the IgE mediated hypersensitivity reaction, also known as the allergic reaction.[29, 30] After being released from the mast cells and basophils it binds to histamine (H_1) receptors on vascular smooth muscle cells and vascular endothelial cells and its activation increases local blood flow and vascular permeability.[31, 32] This completes the initial stage of the inflammatory response. Prolonged inflammation requires the activity of other immune cells. Histamine induced local vasodilatation allows such immune cells greater access to the injured area, while the increased vascular permeability facilitates movement of the immune cells into the tissue.

Eosinophils

Activated eosinophils release leukotrines, prostaglandins, cytokines and chemokines. They also release polypeptides, including major basic proteins, which causes cellular disaggregation and epithelial desquamation. Eosinophil associated corneal damage occurs only in severe chronic allergic conditions.[33, 34]

SECONDARY MEDIATORS

Platelet activating factor (PAF) is a potent eosinophil and neutrophil chemotactic factor and an inflammatory mediator that modulates vascular permeability. PAF has been found in basophils, mast cells, eosinophils, monocytes, polymorphonuclear leucocytes and macrophages. Arachadonic acid is broken down by cyclooxygenase into prostaglandins (D2) and thromboxane, which produce itching and conjunctival redness.[35,36] Leukotrienes are produced due to breakdown of arachadonic acid by lipoxygenase which act by recruiting macrophages.

ALLERGIC CONJUNCTIVITIS

TERMINOLOGY [12]

Conjunctivitis is a nonspecific term used to describe an inflammation of the conjunctiva, which can be caused by a wide range of conditions. It is commonly referred to as "red eye" or "pink eye".[8] Conjunctivitis may result from primary involvement of the conjunctival tissue or may occur secondary to other ocular or systemic conditions that produce conjunctival inflammation.

The conjunctiva, which has a rich vascular supply, abundant immune mediators and direct exposure to the environment, is often involved in immune-mediated and allergic reactions. The various effects of these reactions are responsible for the signs and symptoms present in patients with allergic conjunctivitis. The major categories of allergic conjunctivitis involve Type I hypersensitivity reactions in which the allergen reacts with IgE antibodies, stimulating mast cell degranulation and the release of preformed inflammatory mediators. It includes a spectrum of overlapping conditions that range from intermittent to persistent symptoms and signs variable in severity and presentation.

CLASSIFICATION [37]

Mild, acute allergies include:

• Seasonal allergic conjunctivitis (SAC)

• Perennial allergic conjunctivitis (PAC)

Chronic allergic diseases with the potential for causing significant ocular consequences include:

• Vernal keratoconjunctivitis (VKC)

• Atopic keratoconjunctivitis (AKC)

• Giant papillary conjunctivitis (GPC)

Seasonal Allergic conjunctivitis (SAC) ('hay fever eyes')

This is the most common variety[20, 39]. The seasonal nature of the disease (most common during the spring and summers) is related to the fluctuating levels of aeroallergens such as grass pollens.[40] SAC typically occurs in the fall of spring when grass or ragweed pollens are abundant. Patients typically have a history of other atopic diseases such as eczema or asthma. Classic symptoms include itchy and watery eyes which frequently occur with nasal or pharyngeal symptoms. The conjunctiva is mildly injected, may be swollen and exhibit small papillary hypertrophy. There may be mild lid edema, but no threat to the vision.

Perennial Allergic Conjunctivitis (PAC)

It is clinically similar to seasonal allergic conjunctivitis, but the symptoms persist throughout the year. It is due to chronic exposure to allergens such as dust mites, animal dander, mould spores and feathers.[41] It is less common and tends to be milder than the seasonal form.

SAC and PAC can occur at any age, but patients are typically young, with an average age of 20 to 30 years.[42] The incidence of sensitivity to airborne allergens typically begins around age 8 to 10 years of age. Eighty percent of people who develop allergies have symptoms before the age of 20 years. It affects either gender equally.

Vernal keratoconjunctivitis (VKC)

Vernal keratoconjunctivitis or 'spring catarah' is clinically quiet distinct from seasonal and perennial allergic conjunctivitis. It is uncommon, but occurs in children and young adults, exhibits seasonal variation, with a peak incidence over late spring and summer. It primarily affects boys and onset is generally from about the age of 5 years onwards (mean age 7 years). It is recurrent bilateral disorder in which both IgE and cell mediated immune mechanisms play important roles. It involves upper tarsal conjunctiva and also cornea.

Atopic keratoconjunctivitis (AKC)

It is a rare bilateral disease that typically develops in adulthood (peak incidence 30-50 years) following a long history of eczema. AKC tends to be chronic and unremitting and is associated with significant visual morbidity. It tends to be perennial, although it is often worse in winter. Patients are sensitive to a wide range of airborne environmental allergens.

Giant papillary conjunctivitis (GPC) [43]

Mechanically induced papillary conjunctivitis, the severe form of which is known as giant papillary conjunctivitis, can occur secondary to a variety of mechanical stimuli of the tarsal conjunctivitis. It is most frequently seen with contact lens associated papillary conjunctivitis.[5] Ocular prostheses, exposed sutures and scleral buckles, corneal surface irregularity and filtering blebs can all be responsible.

CLINICAL FEATURES

Common conjunctival symptoms and signs are watering (88%), itching (88%), redness (78%), sore (75%), swollen (72%), and stinging sensation (65%) in the eyes with itching being the hallmark symptom.[44, 45] Involvement of cornea is rare with blurring of vision being the most common symptom.

Clinical signs include

- A milky or a pale pink conjunctiva with vascular congestion that may progress to conjunctival swelling (chemosis) in chronic cases.
- A white exudate may form during the acute state, becoming stringy in the chronic form. Watery discharge is composed of serous exudates.
- Papillae can develop only in the palpebral conjunctiva and in the limbal bulbar conjunctiva where it is attached to the deeper fibrous tissue. A vascular cone is present. Micropapillae form a mosaic like pattern of elevated red dots as a result of the central vascular channel and macropapillae (<1mm) and giant papillae (>1mm) develop with prolonged inflammation. Histology shows folds of hyperplastic conjunctival epithelium with a fibrovascular core and subepithelial stromal infiltration with inflammatory cells. Late changes include superficial stromal hyalinization, scarring and formation of crypts containing goblet cells.

AC can affect both children and adults, often coexisting with other allergic diseases such as asthma, atopic dermatitis or food allergy, though it is particularly associated to allergic rhinitis. Although the eye may be the only organ involved, nasal symptoms and sneezing are frequently reported hence the term “rhinoconjunctivitis” is used in joint reference to both disorders. [4]

DIAGNOSTIC TESTING

The diagnosis of ocular allergies is most often made clinically, however special diagnostic testing can be helpful in some cases.

Skin testing [46]

The "skin-prick test" is an inexpensive way to provide supportive evidence of allergies. This test can also aid in identifying the specific allergen causing the patients problem and can be helpful in avoiding the offending agent. The test is sensitive for systemic allergies, but it is positive in only 20% of patients with ocular allergies.

During the test, allergens such as pollen, dust mite extracts or animal dander are applied to the forearm or back by making shallow pricks with a lancet or a needle. Saline is used as a negative control and histamine is used as a positive control. A skin wheal 2.0 mm or greater in diameter occurring within 15 minutes of exposure is considered a positive test result and indicates that the patient is responsive to the allergen.

Conjunctival provocation test [47]

In the conjunctival provocation test (CPT), allergens are applied topically into the conjunctival sac. The presence of chemosis, hyperemia, and itching within 20 minutes of instillation is considered a positive response. CPT is inexpensive and easy to perform.

Biopsy of conjunctiva [48, 49]

Cytology specimens can be obtained from the conjunctiva, stained and examined microscopically for the presence of eosinophils and mast cells. Eosinophils are not usually present in patients without allergies but are present when an allergic reaction is occurring. Therefore, the presence of eosinophils is considered diagnostic of allergy.

Eosinophils are present during the active phase of VKC, but may be absent following anti-allergy treatment or during the inactive phase of VKC. The presence of mast cells is also highly indicative of active allergy.

Tear fluid analysis [50]

Tear fluid analysis can also be performed. A level of IgE in the tears greater than 16 IU/ml is indicative of allergic conjunctivitis. Tryptase, histamine, leukotrienes and certain cytokines have also been found to be increased in the tears of patients with ocular allergies. Analysis of the tears does not differentiate between different types of ocular allergies.

TREATMENT

Treatment options for ocular allergies include non-pharmacological and pharmacological. The choice of treatment will depend on the severity of the condition.

Non-pharmacological treatment [51]

Non-pharmacological treatment includes allergen avoidance, cold compresses and artificial tears that can provide short-term relief for allergic symptoms. Avoiding the offending allergen will prevent the hypersensitivity reaction from being triggered, but identification of this allergen and complete avoidance is not always possible.

Pollens are the main cause of SAC, preventative measures include limiting outdoor activity during the symptomatic period, closing windows and using air conditioning when in a car or indoors, avoid touching/rubbing eyes after being outdoors, washing hands after being outdoors and wearing close fitting or wrap around sunglasses when outdoors.

As PAC can affect the patient all year round, more thorough avoidance measures are necessary. Dust mite levels in the home can be reduced by using and regularly replacing protective pillow, mattress and covers, washing bedding regularly, vacuum and damp dust entire house, reduce humidity to between 35% and 50% and remove or regularly clean carpets, curtains and any other areas that gather dust. Animal dander can be reduced by eliminating all pets/animals from the home or by keeping them outdoors, regular vacuuming, minimizing exposure to areas that gather animal dander, avoid touching animals, washing hands and avoid eye touching/rubbing after contact with animals and washing all clothes that have come into contact with animals.

Other non-pharmacological interventions include the use of cold compresses, cooled preservative free artificial tears or saline can help in removal and dilution of allergens and can provide ocular lubrication. It also encourages vasoconstriction of the blood vessels to reduce eyelid swelling, chemosis and hyperemia. In addition, the artificial tears may act as a barrier to the pollen allergens to prevent the hypersensitivity response.

Topical medications [2]

Secondary treatment regimens include use of topical medications to provide ease of use, rapid drug delivery and absorption and decreased systemic side-effects. These medications act directly at the site of application. Ophthalmic anti-allergic medications include topical vasoconstrictors, antihistamines, mast cell stabilizers, non-steroidal anti-inflammatory drugs (NSAIDs) and mild steroids.

Topical vasoconstrictors [52]

Vasoconstrictors are sympathomimetic agents like phenylephrine, oxymetazoline and naphazoline. They are highly effective at reducing erythema and lid edema through alfa 1 (α1) receptor stimulation but they have no direct effect on the allergic response. Therefore these agents are often combined with a topical antihistamine, which relieves itching. One to two drops of these agents is administered into the eye four times a day. Oxymetazoline is the most potent vasoconstrictor with quick onset and longer duration. Adverse reactions include burning, stinging and mydriasis. Long-term use of these agents can lead to rebound hyperemia or conjunctivitis medicamentosa.[38]

Antihistamines [52, 53]

Histamine receptors H_1 and H_2 are located widely in the periphery. Stimulation of these receptors cause itching and relaxes the smooth muscles of the blood vessels leading to vasodilation and increased vascular permeability leading to edema. Topical antihistaminics provide faster and quick relief when compared to systemic. These agents include antazoline, pheniramine, levocabastine, emedastine. Levocabastine has rapid and long duration of action with no central nervous system effects. Adverse reactions can include burning and stinging, headache and dry mouth. Combination of a topical antihistamine with vasoconstrictor are more effective in reducing the symptoms than use of the either of the agents alone.[54]

Mast cell stabilizers [55]

Mast cell stabilizers were originally approved for treatment of chronic allergic conditions such as GPC, AKC and VKC, but they have also been found to be effective for treatment of SAC and PAC. They act by inhibiting mast cell degranulation and

thereby reducing the release of inflammatory mediators and suppressing the Type I hypersensitivity reaction. As these drugs acts on the mast cells before degranulation, they have no effect on the inflammatory mediators that are released prior to drug instillation. The mast cell stabilizers indicated for the treatment of AC include sodium cromoglycate, nedocromil and lodoxamide.

Nonsteroidal anti-inflammatory drugs (NSAIDs) [56-58]

NSAIDs inhibit prostaglandin production from arachidonic acid by blocking cyclooxygenase and thus diminish the ocular itching and conjunctival hyperemia and also pain and inflammation associated with AC. These are ketorolac, diclofenac and flurbiprofen. Side effects include stinging and burning sensation on topical administration.

Dual action drugs [59-63]

These drugs exert multiple pharmacological effects such as H_1 receptor antagonist action, stabilization of the mast cells and preventing their degranulation and suppression of activation and filtration of eosinophils. Drugs such as olopatadine, ketotifen, azelastine, epinastine and bepostatine are included in this category. Multiple-acting agents eliminate the need for prescribing two or more separate medications. These agents are typically fast acting (onset less than 15 minutes) due to their antihistamine activity and have a prolonged duration of action (greater than 8 to12 hours) due to their mast cell stabilizing properties. This prolonged duration of action allows twice daily dosing. They are also proved to be safer in children above three years.[51, 55]

Corticosteroids [64-66]

Corticosteroids inhibit phospholipase A, which is used required for the production of arachidonic acid, thus they are potent anti-inflammatory agents. They block the

synthesis of new histamine release by mast cells, inactivate available histamine, inhibit mast cell degranulation and decrease capillary permeability. Topical steroids are often required to treat the acute phase of severe forms of allergic conjunctivitis, such as AKC, VKC and GPC. Once the condition is controlled, the steroid should be tapered and treatment with mast cell stabilizers and antihistamines should be used. These drugs include hydrocortisone, prednisolone, triamcinolone, clobetasone, fluromethalone, rimexalone and loteprednol. Long term side effects includes increased intraocular pressure (IOP), formation of posterior subcapsular cataracts and increased susceptibility to ocular infections and therefore patients should be closely monitored for these potential side-effects. These agents should be considered in severe cases and when other agents have been found to be ineffective.

Topical immunosuppressive agents [67-69]

Topical immunosuppressive agents are used mainly as alternative therapies for patients who have sever and suffer from chronic forms of conjunctivitis like VKC or AKC. These agents inhibit histamine release, mast cell degranulation, T-lymphocyte proliferation, cytokine production and the responsiveness of cells to cytokines. They are cyclosporine and tacrolimus.

PHARMACOLOGY OF OLOPATADINE AND KETOTIFEN

Both olopatadine and ketotifen are second generation anti histaminics and mast cell stabilizers. Histamine$_1$ (H_1) receptors are expressed primarily on vascular endothelial and smooth muscle cells which mediate inflammatory and allergic reactions. Tissue-specific responses to H_1 receptor stimulation include edema, bronchoconstriction and sensitization of primary afferent nerve terminals. H_1 antihistamines strongly block the increased capillary permeability necessary for the manifestation of edema and wheals. The anti-inflammatory property is attributable to suppression of the NF-κβ pathway.

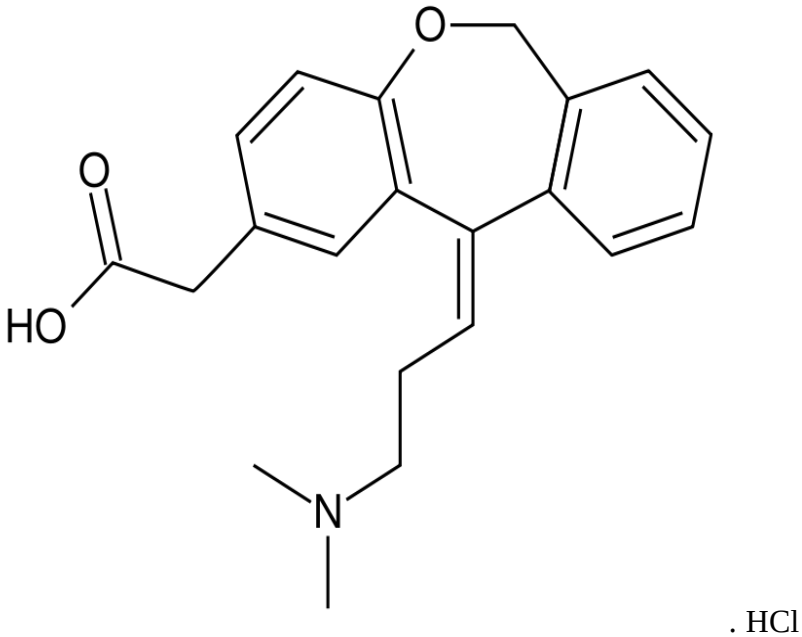
The H_1 receptor activates G protein–mediated hydrolysis of phosphatidylinositol, leading to increased inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 triggers the release of Ca^{2+} from intracellular stores, increasing cytosolic Ca^{2+} concentration and activating downstream pathways. DAG activates protein kinase C, leading to phosphorylation of numerous cytosolic target proteins. In some tissues, such as bronchial smooth muscle, the increase in cytosolic Ca^{2+} causes smooth muscle contraction by Ca^{2+}/calmodulin-mediated phosphorylation of the myosin light chain. In other tissues, especially precapillary arteriolar sphincters and postcapillary venules, the increase in cytosolic Ca^{2+} causes smooth muscle relaxation by inducing the synthesis of nitric oxide. H_1 receptor stimulation also leads to the activation of NF-κβ, an important and ubiquitous transcription factor that promotes the expression of adhesion molecules and pro inflammatory cytokines.[70]

History [71]

Histamine blocking activity was first detected in 1937 by Bovet and Staub in one of the series of amines with a phenolic ether function. The substance, 2-isopropyl-5-methylphenoxy-ethyldiethyl-amine, protected guinea pigs against several lethal doses of histamine, antagonized histamine-induced spasm of various smooth muscles and decreased the symptoms of anaphylactic shock. This drug was too toxic for clinical use, but by 1944, Bovet and his colleagues had described pyrilamine maleate, which is still one of the most specific and effective histamine antagonists. Later the discovery of the highly effective histamine antagonists diphenhydramine and tripelennamine followed. In the 1980s, non-sedating H_1 receptor antagonists were developed for treatment of allergic diseases. Despite success in blocking allergic responses to histamine, they failed to inhibit a number of other responses, notably gastric acid secretion. The discovery of H_2 receptors and its antagonists by Black and colleagues provided a new class of agents that antagonized histamine-induced acid secretion.

CHEMICAL STRUCTURE [72, 73]

Olopatadine hydrochloride [$C_{21}H_{23}NO_3HCl$] is a 11-[(Z)-3-(dimethylamino)-propylidena]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid, hydrochloride, a tricyclic compound. It is a white, crystalline, water soluble compound with a molecular weight of 373.88. Olopatadine 0.1% and 0.2% ophthalmic solution is an aqueous solution containing 1 mg/ml and 2 mg/ml of olopatadine hydrochloride respectively with benzalkonium chloride 0.01% as a preservative. It is FDA approved for treatment of ocular itching associated with allergic conjunctivitis.



. HCl

Fig. 3- Chemical structure of Olopatadine HCl

Ketotifen fumarate [$C_{19}H_{19}NOS,C_4H_4O_4$] 4-(1-Methylpiperidin-4-ylidene)-4,9-dihydro-10H-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one is a white to brownish-yellow, fine crystalline powder. It is sparingly soluble in water, slightly soluble in methanol and very slightly soluble in acetonitrile with a molecular weight of 425.5. Ketotifen fumarate 0.025% is a sterile ophthalmic solution for topical administration to the eye. 1.0 ml contains 345µg ketotifen fumarate corresponding to 250µg ketotifen. Benzalkonium chloride 0.1 mg/mL is used as preservative.

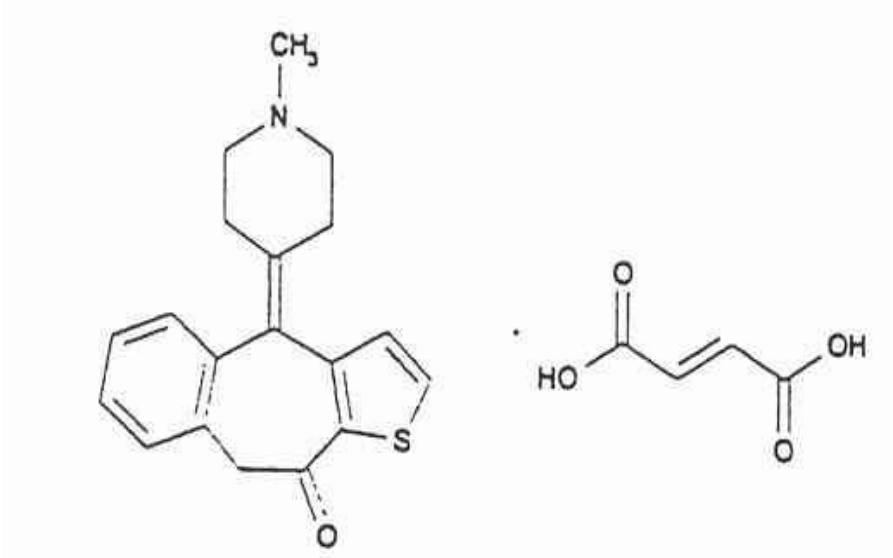


Fig. 4- Chemical structure of Ketotifen

MECHANISM OF ACTION

Olopatadine and ketotifen inhibits the binding of histamine to H_1 receptor, with olopatadine having superior H_1 receptor selectivity. They have also been shown to stabilize human conjunctival mast cells and inhibit the immediate allergic response to an antigen challenge but do not relieve an allergic response once it has been initiated. It decreases the activity of mast cells, preventing release of their inflammatory mediators upon antigen challenge. For this reason, olopatadine and ketotifen are also viewed as a "mast-cell stabilizing agent." The release of inflammatory mediators from eosinophils, neutrophils, monocytes, macrophages, and lymphocytes is also inhibited. The underlying molecular mechanism may involve inhibition of chloride ion transport, which in turn affects calcium gating to prevent mediator release from intracellular granules.

PHARMACOLOGICAL ACTIONS [70]

Smooth Muscle

Both these drugs inhibit the effects of histamine on smooth muscles, especially the bronchoconstriction. They also inhibit both the vasoconstrictor effects of histamine and to a degree, the more rapid vasodilator effects mediated by activation of H_1 receptors on endothelial cells due to synthesis and release of nitric oxide (NO).

Capillary Permeability [74]

H_1 antagonists strongly block the increased capillary permeability and formation of edema and wheal caused by histamine. Olopatadine has ability to inhibit antigen and histamine stimulated conjunctivitis, reduced vascular permeability at 5 and 24 hrs after treatment, indicating it has long duration of action.

Flare and Itch [75]

H_1 antagonists suppress the action of histamine on nerve endings, including the flare component of the triple response and itching caused by intradermal injection. If histamine is injected intradermally, it elicits a characteristic phenomenon known as the "triple response". It consists of a localized red spot, extending for a few millimeters around the site of injection, that appears within a few seconds and reaches a maximum in about a minute; a brighter red flush or flare extending about 1 cm or so beyond the original red spot and developing more slowly; and a wheal that is discernible in 1 to 2 minutes and occupies the same area as the original small red spot at the injection site. The red spot results from the direct vasodilatory effect of histamine, the flare is due to histamine induced stimulation of axon reflexes that cause vasodilation indirectly, and the wheal reflects histamine's capacity to increase capillary permeability.

Exocrine Glands

H_1 antagonists do not suppress gastric secretion; they do inhibit histamine evoked salivary, lacrimal and other exocrine secretions. The antimuscarinic properties of many of them may contribute to decreased secretion in cholinergic innervated glands and reduce ongoing secretion.

Immediate Hypersensitivity Reactions: Allery and Anaphylaxis

During hypersensitivity reactions, histamine is one of the potent autacoid released. Edema formation and itch are effectively suppressed. Other effects such as hypotension are less antagonized. This may be explained by the participation of other types of histamine receptors and by effects of other mast cell mediators, chiefly eicosanoids. Bronchoconstriction is decreased.

Central Nervous System

The first-generation H_1 antagonists can both stimulate and depress the CNS. Patients may experience an antihistamine "hangover" in the morning, resulting in sedation with or without psychomotor impairment. Thus, the development of second-generation "non sedating" antihistamines was an important advance as they do not cross the blood-brain barrier.

Anticholinergic Effects

Many of the first-generation H_1 antagonists inhibit responses to acetylcholine mediated by muscarinic receptors which may manifest during clinical use, whereas the second generations do not possess this property.

Other actions of Olopatadine

Mast cell stabilization [76-78]

Olopatadine inhibits anti-IgE antibody-mediated release of TNF-α from human conjunctival mast cells. It also significantly decreases the mast cell supernatant mediated up regulation of ICAM (intracellular adhesion molecules)-1 on human conjunctival epithelial cells in vitro. This effect may be mediated through a TNF-α specific mechanism and could contribute to the long duration of anti-allergic activity for the drug. Concentrations of olopatadine (0.1%) maintain normal mast cell and corneal epithelial cell membrane function. Its restricted interaction with membrane phospholipids limits the degree of membrane perturbation and release of intracellular constituents, including histamine, lactate dehydrogenase (LDH) and hemoglobin. This is believed to account for its topical ocular tolerability and patient compliance.

Additional anti- allergic effects of olopatadine [79, 80]

Olopatadine pretreatment of conjunctival mast cells inhibits the mediator release associated with eosinophil adhesion to conjunctival epithelial cells and eosinophil degranulation. In conjunctival epithelial cell cultures, olopatadine inhibits histamine induced production of IL-1, IL-6, IL-8 and granulocyte macrophage colony stimulating factor (GM-CSF).

Olopatadine has been shown to have other interesting anti-allergic properties. In a mouse model of contact hypersensitivity, olopatadine reduced the ability of Langerhans cells to present hapten to primed T cells, indicating that this drug decreases contact hypersensitivity by interfering with the antigen- presenting ability of Langerhans cells.
In an antigen induced conjunctivitis model in rats olopatadine 0.1% and 0.2% significantly inhibited substance P release from the conjunctiva.

Other action of ketotifen [81]

Ketotifen inhibits the passive cutaneous anaphylaxis (PCA) and the histamine-induced reactions. It has both antihistaminic and anti-allergic properties, and its anti-allergic action does not depend on its histamine blocking property. The release of mediators, in particular histamine and slow reacting substance of anaphylaxis (SRS-A) play a major role in the pathogenesis of asthma. SRS-A, a mixture of leukotrienes, is not stored but formed from arachidonic acid upon cell stimulation. In addition, SRS-A is also produced and released by cells which do not store or release histamine. The release of SRS-A is inhibited to a large extent by pre incubation with ketotifen determined by bioassay.

Ketotifen has also shown to inhibit the influx of calcium ions which follows sustained depolarization of the smooth muscle cell membrane. This could be relevant to the anti-allergic effect of ketotifen since contractions induced by anaphylaxis or by liberated autocoids involve depolarization of the smooth muscle membrane.

PHARMACOKINETIC PROPERTIES [73, 81-83]

Olopatadine

Absorption: After single oral administration of olopatadine (5 – 80mg), it is absorbed rapidly, reaches Cmax values at 0.5 – 2 h, and decreases thereafter. The elimination half-life (t½) is 8 - 12 h. After oral administration at a dose of 80 mg, the percentage of N-oxide (M3) and N-monodesmethyl form (M1) in plasma were about 7% and 1% respectively of the unchanged drug.

Systemic exposure to olopatadine following ocular administration is minimal, with plasma concentrations ranging from 0.5 ng/ml to 1.3 ng/ml. The protein binding (albumin) in humans were in a range of 54.7% - 55.2%.

Metabolism: The radioactivity in the plasma, urine and feces after oral administration of ^{14}C olopatadine to rats and dogs was mainly detected as the unchanged drug. The metabolic pathway of olopatadine after oral administration is assumed to consist of:

- N demethylation at the side chain moiety,
- Hydroxylation at the dibenzoxepine ring,
- Sulfate-conjugation of the hydroxylated metabolite and
- N-oxidation of the side chain moiety.

Olopatadine has no inhibitory effect on the drug-metabolizing activities catalyzed by these isoforms of cytochrome P450. Results of a study conducted on rats indicated that CYP3A4 was mainly involved in the generation of M1. On the other hand, the generation of M3 was mainly catalyzed by CYP1A2 in the system containing human liver microsome.

Elimination: In contrast to many other anti allergic drugs that are eliminated by hepatic clearance, 60% - 70% of olopatadine is eliminated by the renals. The mean ratios of urinary excretion of M1 and M3 were 0.17% – 1.67% and 2.23% – 4.62% of dose, respectively. The metabolite M2 was not detected in the urine. This indicates that olopatadine is excreted mainly through a renal route without receiving extensive metabolism after absorption and, therefore the drug-drug interaction in drug metabolism is very unlikely to occur. Plasma concentrations are expected to be greater in patients with severe renal impairment compared with healthy adults. However, since plasma concentrations after ocular administration are 50 – 200 folds lower than those following well-tolerated oral doses, dose adjustments are not necessary in the elderly or in the renal impaired population.[78]

Ketotifen

Ketotifen fumarate is almost completely absorbed from the gastrointestinal tract after oral doses, but bioavailability is reported to be only about 50% due to hepatic first-pass metabolism. Peak plasma concentrations occur 2 to 4 hours after an oral dose. It is mainly excreted in the urine as inactive metabolites with a small amount of unchanged drug and the terminal elimination half-life is about 21 hours.

USES

1. Seasonal allergic conjunctivitis [2, 84]
2. Perennial allergic conjunctivitis [2]
3. Vernal keratoconjunctivitis [2]
4. Atopic keratoconjunctivitis [2]
5. Giant papillary conjunctivitis [85, 86]
6. Allergic rhinitis [87, 88]
7. Prophylactic management of asthma [89, 90]
8. Chronic urticaria [91, 92]

ADVERSE EFFECTS [93, 94]

Olopatadine: Headache, stinging or burning of the eye and blurring of vision occurs after ocular use. Common adverse effects include bitter taste and somnolence.

Ketotifen: Irritation, pain, stinging sensation, blurring of vision, photophobia, dry eyes, headache and punctate keratitis are commonly reported after topical application to the eye.

Adverse effects common to both

On instillation patient may experience eye irritation, eye pain, blurred vision (during instillation), dry eye, eyelid disorder and photophobia. Gastrointestinal effects include nausea vomiting, diarrhoea or epigastric pain. Rash, eczema and urticaria and hypersensitivity reactions including bronchospasm, angioedema and anaphylaxis may also occur. Blood disorders are rare includes agranulocytosis, leucopenia, haemolytic anaemia, and thrombocytopenia. Convulsions, sweating, myalgia, paraesthesias,

extrapyramidal effects, tremor, sleep disturbances, depression, confusion, tinnitus, hypotension and hair loss are very rare.

DOSAGE

These eye drops are available in two concentrations as Olopatadine 0.1% and 0.2% ophthalmic solutions. Instill two drops of the solution in the affected eye two times a day till the symptoms are relieved. Ketotifen 0.025% and 0.05% ophthalmic solution to be instilled twice a day till the symptoms subsides.

MATERIALS AND METHODS

MATERIALS AND METHODS

The study was conducted on outpatients attending the Department of Ophthalmology at R.L. Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar. Patients clinically diagnosed with allergic conjunctivitis were recruited for the study. The duration of the study was from January 2012 to June 2013.

Inclusion criteria

1. Patients of either gender aged above 8yrs.
2. Those diagnosed with seasonal allergic conjunctivitis.

Exclusion criteria

1. Patients suffering from bacterial, chlamydial, viral, giant papillary, phlyctenular, purulent and membranous conjunctivitis.
2. Those with dry eye, blepharitis, uveitis, keratitis, ocular trauma within 3 months prior to recruitment.
3. Patients who have undergone ocular surgery within 3 months prior to recruitment.
4. Patients with retinal detachment, diabetic retinopathy or progressive retinal disease.
5. Those receiving corticosteroids and immunosuppressants.
6. Those who have taken treatment with mast cell stabilizers, NSAIDs, anti histaminics for conjunctivitis within one month prior to recruitment.
7. History of hypersensitivity to olopatadine and ketotifen.
8. Pregnant and lactating women.

Ethical clearance was obtained from institutional ethics committee. Patients who were willing to give the written informed consent were included in the study. A proforma containing detailed information of each patient was designed according to the study protocol.

Patients clinically diagnosed with allergic conjunctivitis by Ophthalmologist were included in the study. They were randomly divided by lottery method into two groups with minimum of 60 patients in each. Relevant data was taken from these patients in terms of name, age, gender, address, occupation, educational status, hospital number, date of first visit to the hospital, the duration of complaints, aggravation factors and seasonal variation of the symptoms, family history of asthma, previous history of allergic conjunctivitis (AC) and personal history of smoking/alcohol intake, diabetes mellitus/ hypertension/ bronchial asthma.

On clinical examination the following findings were recorded: redness in the eyes, presence of papillae over the conjunctiva, vision, fundus and eye lids. The patient's symptoms and signs were assessed using a scoring scale. The scores range from 0 to 16 (Table 1).[94] The patient's quality of life (QOL) was assessed using a questionnaire consisting of 15 questions and the scores range from 0 to 90 (Table 2).[95] Patients in group A received Olopatadine HCl 0.1% ophthalmic solution and group B Ketotifen fumarate 0.025% ophthalmic solution. They were instructed to instill 2 drops into the affected eyes twice daily and to maintain a dairy to record the timing of instillation of their medication.

Assessment of symptoms and signs scoring was carried out on the 1st visit (baseline), 4th day, 15th day and if the clinical signs persisted they were evaluated on

the 30th day. QOL questionnaire was administered to the patients on the 1st, 4th and the 15th day. During each visit they were requested to carry their diary and their compliance to the medication was recorded. Patients were examined for response to treatment and improvement in their symptoms and signs. Adverse effects if any were recorded at each visit. Cost effectiveness was analyzed by calculating the amount spent by the patient for complete recovery from symptoms and signs of AC.

Table 1 - Allergic conjunctivitis symptoms and signs scoring

Score	Symptoms and Signs
Itching	
0	Absent
1	An intermittent tickle sensation involving more than just the inner corner of the eye
2	A mild continuous itch not requiring eye rubbing
3	A definite itch, the subject would like to be able to rub the eye
4	An incapacitating itch which would require significant eye rubbing
Tearing	
0	Absent
1	Mild: (eyes feel slightly watery)
2	Moderate: (occasional need to wipe the eyes)
3	Severe: (tears rolling down the cheeks)
Hyperemia	
0	Absent (vessels normal)
1	Mild (some vessels definitely injected above normal)
2	Moderate (diffusely red eye with individual vessels dilated but still discernible)
3	Severe (intensely red eye with intensive dilatation of conjunctival vessels which are easily visible)
Eyelid Swelling	
0	Absent
1	Mild (lids are little puffy)
2	Moderate (frank swelling of upper and lower eyelid)
3	Severe (eyelids are definitely swollen)
Chemosis	
0	Absent or visually not detectable
1	Visually evident, raised conjunctiva especially at limbal area
2	Ballooning of conjunctiva
Papillae	
0	Absent
1	Present

Table 2 - Quality of life questionnaire

Activities

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15
1.																					
2.																					

Sleep

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15
3.Difficulty getting sleep																					
4. Lack of good night's Sleep																					

Practical problems

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15
5.Inconvenience of having to carry tissue or handkerchief																					
6. Need to rub nose or eyes																					
7.Need to blow nose repeatedly																					

Nasal Symptoms

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15
8.Running Nose																					
9. Post nasal Drip																					

Eye Symptoms

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15
10.Itchy Eyes																					
11.Watey Eyes																					
12.Sore Eyes																					
13.Swollen eyes																					

Emotional

	None of The Time			Hardly Any Time At All			A Small Part Of The Time			Some Part Of The Time			A Good Part Of The Time			Most Of The Time			All Of The Time		
	0			1			2			3			4			5			6		
Day / Act.	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15
14. Irritable																					
15.Embarrassed by your symptom																					

STATISTICAL ANALYSIS

To detect the mean difference of 0.35 in the itching score on day 7 with the effect size of 1.2, α error 5%, with 80% power and 10% dropout rate the sample size required in each group was 32 patients. The demographic data were analyzed using descriptive statistics and expressed as mean ± standard deviation. Continuous data within and between the groups were analyzed using paired and unpaired t-test respectively. The allergic conjunctivitis and quality of life scores within and between the groups was analyzed using Wilcoxon Signed Rank Test and Mann-Whitney U test respectively. Categorical data was analyzed by Chi-square test. P-value of 0.05 or less was considered statistically significant.

RESULTS

RESULTS

A total number of 120 patients who satisfied the inclusion criteria and clinically diagnosed by Ophthalmologists as allergic conjunctivitis were included in this study. Patients were randomized to Group A (n=60), who received topical olopatadine HCl 0.1%. They were instructed to instill two drops twice daily in both eyes. Group B (n=60) patients were instructed to instill ketotifen fumarate 0.025% two drops four times daily. Fifty five patients in group A and 56 in group B completed the study.

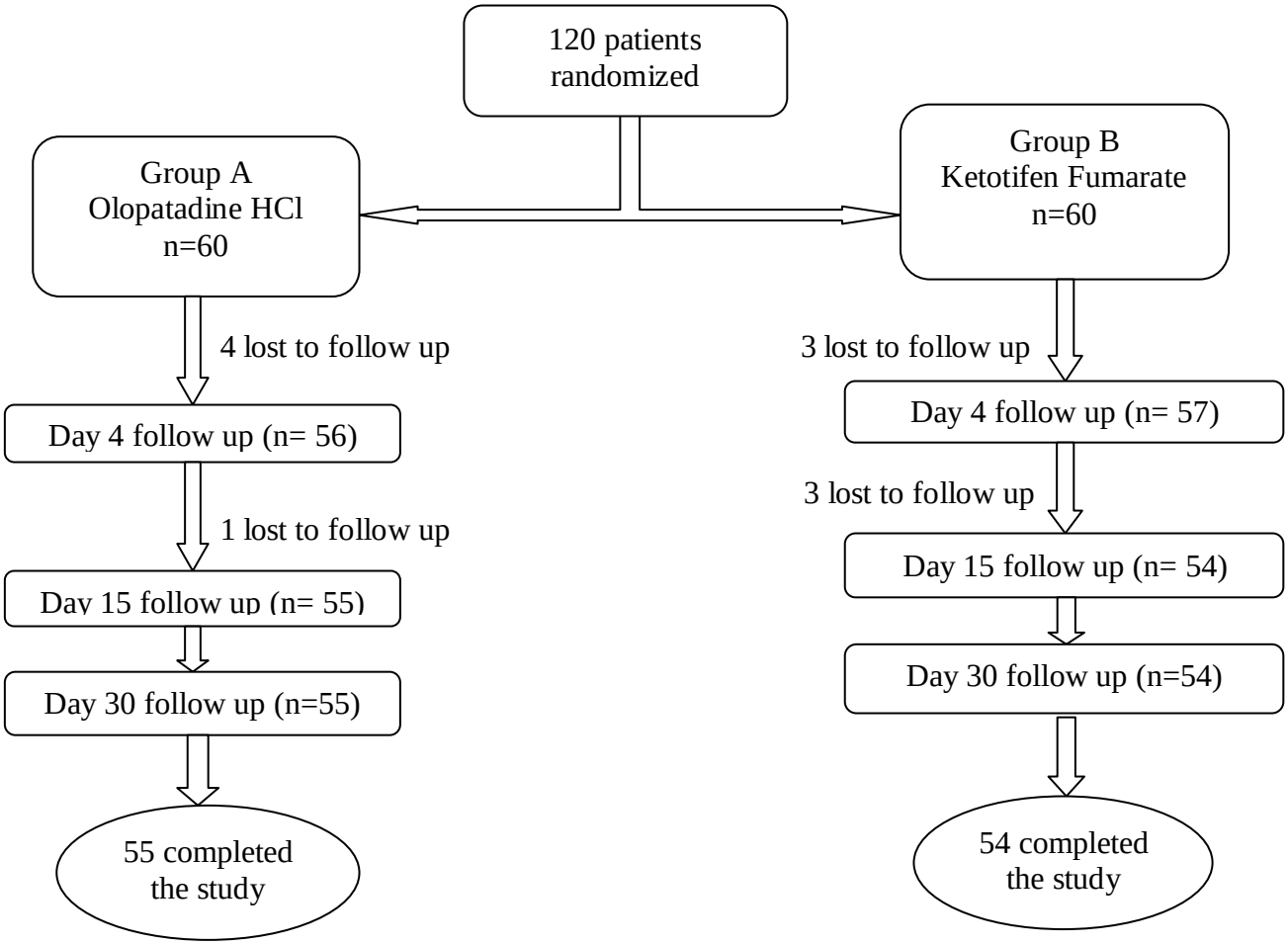


Fig.5 Flow chart representing randomization and follow up of patients

Table 3: Demographic Data

		Olopatadine HCl n= 60	Ketotifen Fumarate n= 60	p value
Gender	**Male (%)**	38 (63.3%)	29 (48.3%)	0.098
	Female (%)	22 (36.7%)	31 (51.7%)	
Age (Mean±SD)		36.35 ± 11.91	36.20 ±12.70	0.947

There were 67 males and 53 females in the present study. The demographic details between the groups were comparable.

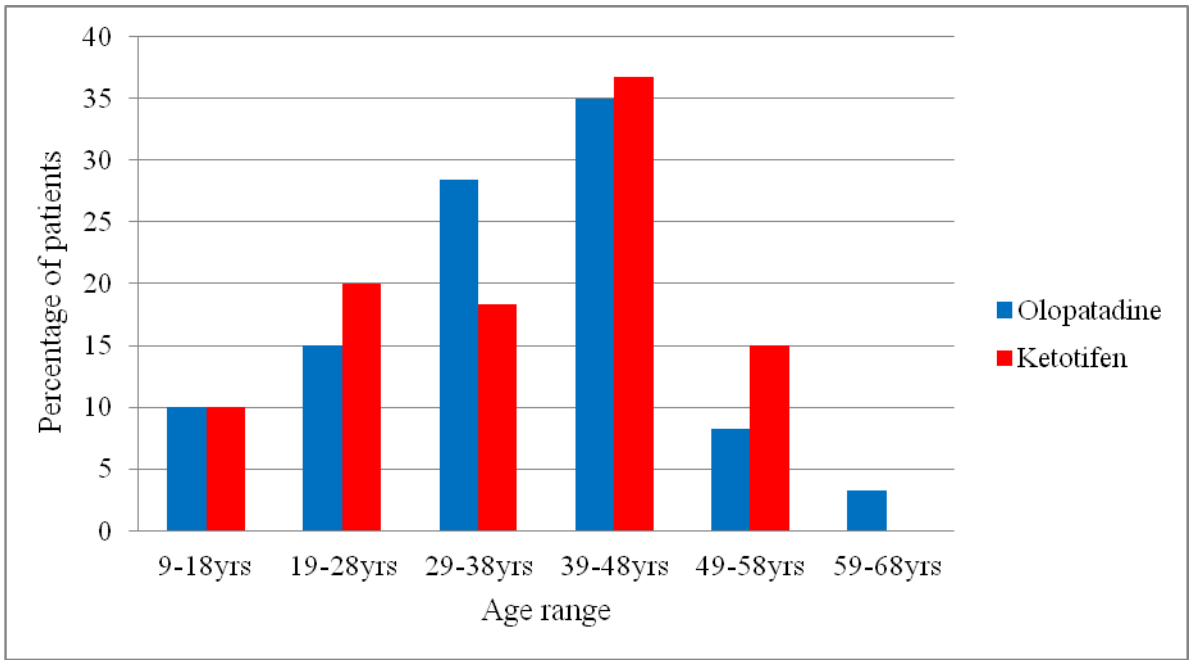


Fig.6 Percentage of patients in different age groups

Majority of the patients in both the groups were in the age of 39-48 years.

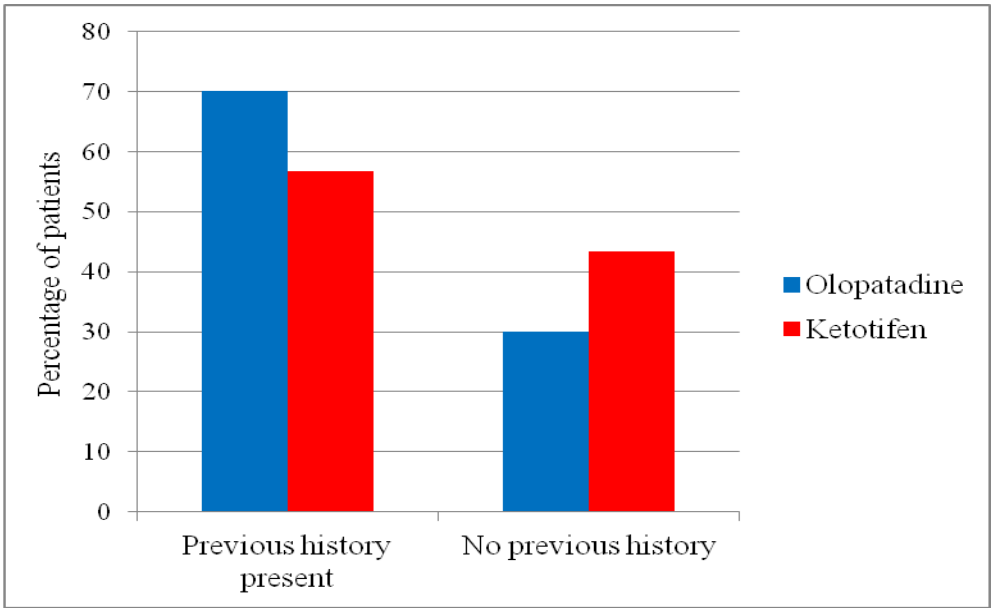


Fig.7 History of previous allergic conjunctivitis

Past history of allergic conjunctivitis was present in 42 and 34 patients in each of the groups.

The aggravating factors for allergic conjunctivitis were seasonal variation (summer 25 and 16 patients) and dust (17 and 18 patients).

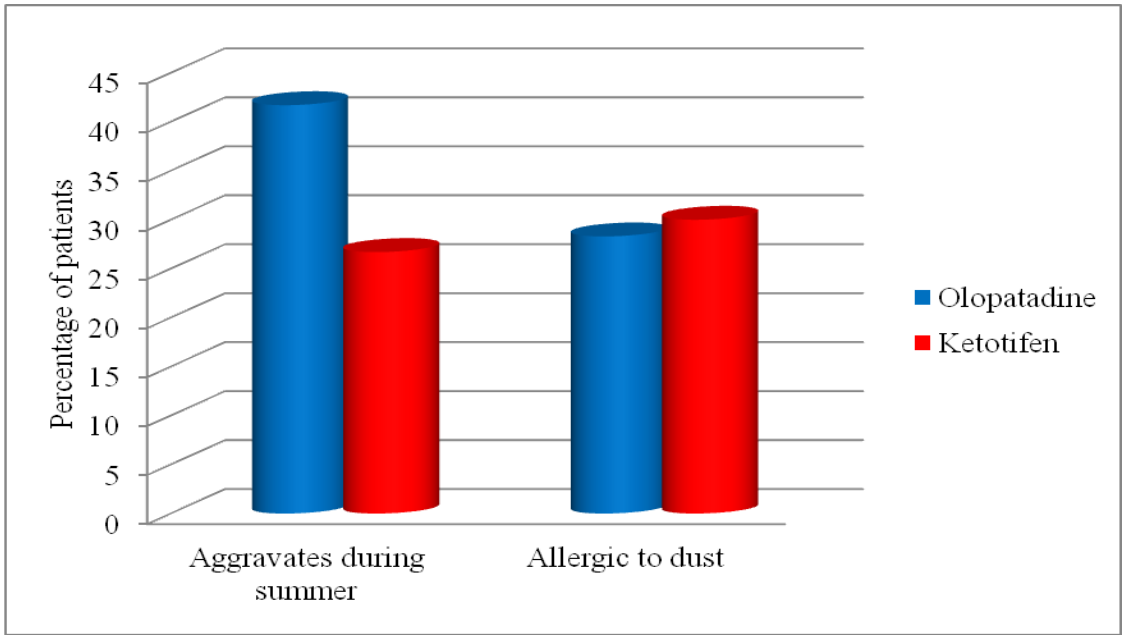


Fig.8 Percentage of patients with history of aggravating factors

Table 4: Baseline AC and QOL scores

Baseline scores	Olopatadine HCl		Ketotifen Fumarate		p value
	Mean±SD	Median (Range)	Mean±SD	Median (Range)	
Itching Score	3.9±0.30	4 (3-4)	3.72±0.45	4 (3-4)	0.01
Tearing score	2.82±0.39	3 (2-3)	2.85±0.40	3 (1-3)	0.48
Hyperemia	2.60±0.52	3 (1-3)	2.52±0.50	3 (2-3)	0.31
Eyelid swelling	0.23±0.427	0 (0-1)	0.13±0.34	0 (0-1)	0.15
Papillae	1±0.00	1 (1-1)	1.00±0.00	1 (1-1)	1.00
Total AC Score	10±1.04	10 (9-12)	10.23±1.01	10 (9-12)	0.08
QOL Score	35.73±8.55	36 (19-54)	32.98±7.41	32 (20-50)	0.10

The baseline allergic conjunctivitis and quality of life scores were comparable between the groups except itching score (p= 0.01). None of the patients had signs of chemosis at the time of recruitment.

Table 5: Individual and total AC scores at follow up visits

Symptoms and Signs	Olopatadine HCl				Ketotifen Fumarate			
	Mean±SD			p value	Mean±SD			p value
	Day 0	Day 4	Day 15		Day 0	Day 4	Day 15	
Itching	3.9±0.30	1.98±0.83*	0#	0.001	3.72±0.45	2.37±0.73*	0.40±0.49#	0.001
Tearing	2.82±0.39	1.13±0.74*	0#	0.001	2.85±0.40	1.63±0.68*	0.05±0.22#	0.001
Hyperemia	2.60±0.52	0.73±0.68*	0	0.001	2.52±0.50	1.25±0.62*	0	0.001
Lid swelling	0.23±0.42	0	0	0.001	0.13±0.34	0	0	0.005
Papillae	1±0.00	0.85±0.36	0#	0.001	1.00±0.00	0.95±0.22	0.37±0.48#	0.001
Total Score	10±1.04	4.72±2.10*	0#	0.001	10.23±1.01	6.13±1.8*	0.82±0.87#	0.001

* p = 0.001 comparison between groups on 4th day

p= 0.001 comparison between groups on 15th day

Patients receiving either olopatadine or ketotifen have shown significant reduction (p=0.001) in all the individual and total AC scores by 4th and 15th day compared to baseline. Between group analysis showed that by fourth day itching, tearing, hyperemia and total allergic conjunctivitis scores reduced significantly (p=0.001) in patients who received olopatadine, but not eyelid swelling and papillae. Similarly by 15th day there was significant reduction (p=0.001) in itching, tearing, papillae and total AC score in patients who received olopatadine but reduction in hyperemia and eyelid swelling were similar in both the groups.

Table 6: QOL score at follow up visits

	Day 0	Day 4	Day 15	p value
Olopatadine HCl	35.73±8.55	12.90±5.17	0	0.001
Ketotifen Fumarate	32.98±7.41	12.93±5.10	0	0.001
p value	0.10	0.81	1.00	

When the mean QOL score at two follow up visits was compared with baseline in patients receiving either of the drugs a significant reduction was seen in both the groups, but there was no significant difference in the scores between the groups.

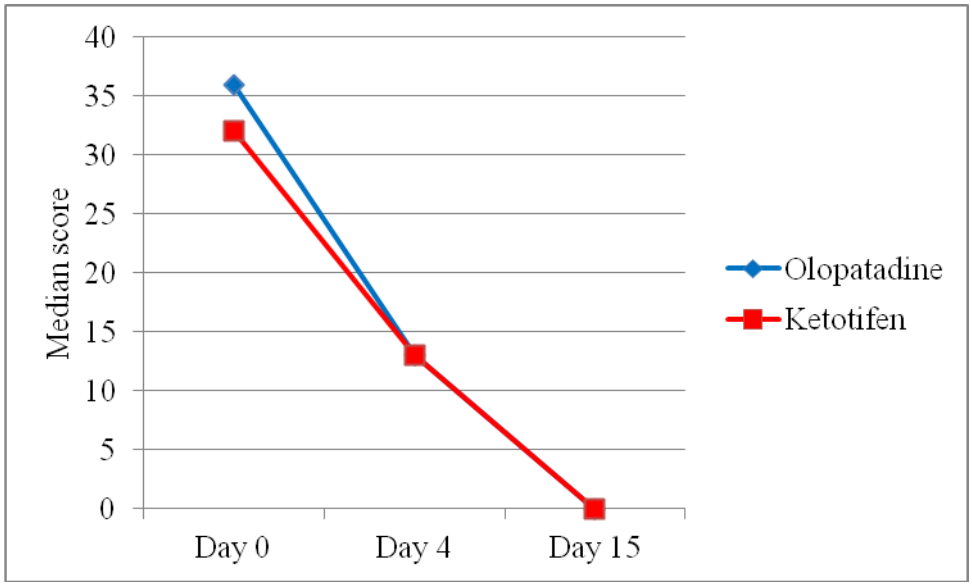


Fig.9 QOL scores at follow up visits

Table 7: Adverse effects to medications

	Headache	Burning sensation in the eyes
Olopatadine HCl	4	2
Ketotifen Fumarate	8	3

A total of 10% and 18.3% reported adverse reactions with olopatadine and ketotifen respectively.

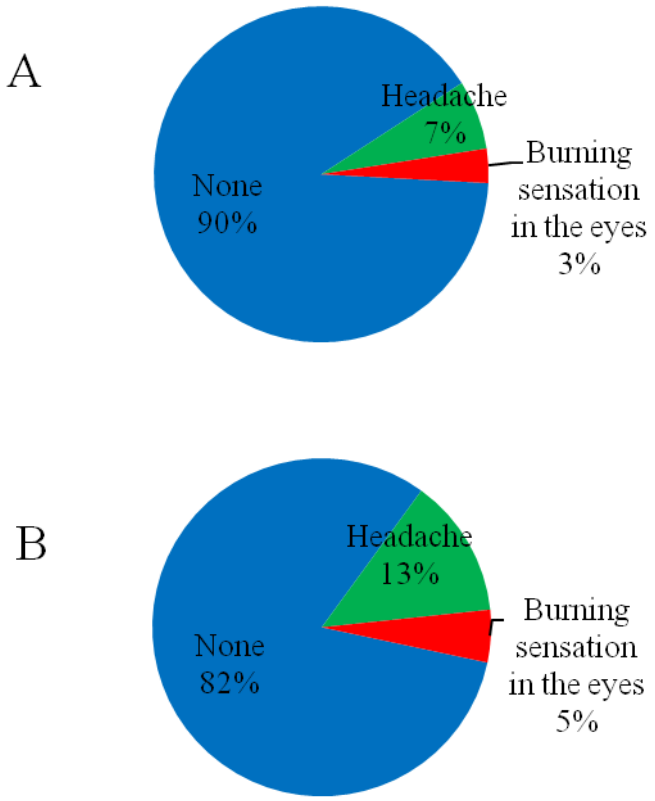


Fig.10 Adverse reactions to olopatadine HCl (A) ketotifen fumarate (B)

Cost of the treatment

The cost of one olopatadine HCl vial was 84 rupees and each patient required one vial therefore the cost per patient was 84 rupees. Whereas one vial of ketotifen fumarate was 57 rupees and 32 patients required two vials therefore the cost for these patients was 114 rupees.

DISCUSSION

DISCUSSION

Conjunctivitis due to non infectious stimuli includes seasonal and perennial allergic conjunctivitis. This condition affects the individuals of all the age groups mainly children. In seasonal allergic conjunctivitis (SAC) the symptoms aggravate due to seasonal variations or in the presence of dust and affect both eyes. Ocular symptoms and signs include itching which is the hallmark of ocular allergy, tearing, conjunctival hyperemia, eyelid swelling, chemosis and foreign body sensation. If left untreated it may become severe, and the discomfort will hamper their quality of life.

Various modalities of treatment include non pharmacological and pharmacological therapy. Non pharmacological methods are allergen avoidance, cold compresses and artificial tears that can provide short-term relief of allergic symptoms. Various drugs used in the treatment of allergic conjunctivitis (AC) are topical medications like vasoconstrictors (phenylephrine, oxymetazoline and naphazoline), antihistamines (antazoline, pheniramine, levocabastine, emedastine), mast cell stabilizers (sodium chromoglycate, nedocromil and lodoxamide), non-steroidal anti-inflammatory drugs (ketorolac, diclofenac and flurbiprofen), steroids (hydrocortisone, prednisolone, triamcinolone, clobetasone, fluromethalone, rimexalone and loteprednol) and drugs with dual action (olopatadine, ketotifen, azelastine, epinastine and bepostatine). Dual action drugs like mast cell stabilizers and anti histaminics are now preferred over the others because of quicker relief, minimal dosing and fewer side effects.

In the present study it was seen that out of 120 patients who were clinically diagnosed with allergic conjunctivitis 56% were males and 44% females (Table 3). The male to female ratio was 1.2:1. A study conducted in Ghana has showed that percentage

of females (61.8%) affected with AC was higher and in another study carried out in Nigeria including 150 students between 5-15 years it was 59% the probable reason being hormonal changes in females.[96, 97]

In our study the mean age of the patients receiving olopatadine and ketotifen were similar (Table 3). We observed that many patients suffering from AC were in the age group of 39-48 years (Fig. 6). Although it can affect individuals of any age group, it is more common in childhood. In Khaled et al study which was conducted to evaluate the global prevalence of rhinoconjunctivitis in children the prevalence was found to be 14.6% in the age group of 13 – 14 years and 8.5% in 6 to 7 years.[98]

The patients in this study had previous history of AC (Fig. 7) and percentage of patients who reported that the symptoms of allergic conjunctivitis aggravated during summer and in presence of dust have been shown in Fig. 8, those receiving olopatadine had more patients with these aggravating factors. Study conducted by Palmares et al showed that around 85% had previous episodes of allergic conjunctivitis and 16% were suffering from bronchial asthma.[99] However in our study patients suffering from bronchial asthma were excluded. A Nigerian study done in primary school children has shown that the disease was more common during harmattan (a dry and dusty West African trade wind) season due to presence of dust and pollen in the atmosphere.[97]

Table.4 represents the individual and total allergic conjunctivitis scores which were comparable between the groups at baseline except the itching score which was higher in patients receiving olopatadine and none had signs of chemosis. Itching was the most common presenting complaint of the patients. On treatment with olopatadine 0.1% there was a significant reduction seen in the itching score on 4^{th} and 15^{th} day follow up. The

patient was completely free of the symptom by the 30th day. Similar finding was seen in a study conducted in Hungary which included both adults and children, the itching scores reduced from 1.6 to 0 and 2.5 to 0.2 respectively at the end of 14 days. This study also concluded that olopatadine was safe to use in children.[100] In conjunctival allergen challenge human model olopatadine 0.1% and 0.2% were compared and there was no significant difference in the itch score between doses, but a significant reduction was observed at 24 hours with both dosages when compared to placebo.[101] Study in Japanese patients with seasonal allergic conjunctivitis, pre treatment with olopatadine has significantly reduced the itching scores, they have attributed this to mast cell stabilizing property of the drug.[102] The tearing score with olopatadine was significantly reduced at all follow up visits (Table 5). Similar results were obtained when olopatadine 0.1% was compared with sodium chromoglycate 2%.[103] In our study olopatadine has reduced hyperemia significantly and similar findings were observed when it was compared with ketorolac.[104]

Eyelid swelling causes a lot of discomfort to the patient, this was reduced by 4th of treatment (Table 5), and similar results were observed when olopatadine 0.1% was compared with cromolyn sodium 2%.[105] Papillae is one of the sign in AC, there was significant reduction by fourth day of treatment with olopatadine. A complete reduction in the score was observed in 15% of the patients by the 4th day, whereas by 15th day complete reduction was seen in all the patients. There was a reduction in the total allergic conjunctivitis scores at all the follow up visits compared to baseline (Table 5).

In patients receiving ketotifen a reduction in all the individual and total AC score was seen at each follow up visit (Table 5). Only in 46.6% of the patients the score

reduced to zero by 15th day. A study has shown that ketotifen 0.05% reduced itching, stinging and tearing after 10 days in 60% - 80% of the patients.[106] When ketotifen was compared with levocabastine and placebo, it was seen that ketotifen was most effective during the first four days and it effectively reduced the itching, hyperemia and the tearing score, however the eyelid swelling score also reduced but it was not statistically significant compared to levocabastine and placebo.[107] Our observation was that reduction in papillae score took longer time and 63% patients showed complete reduction only by 15th day.

When we compared the results of both the drugs olopatadine significantly reduced the itching, tearing, hyperemia and the total AC scores by 4th day and eyelid swelling and papillae by 15th day compared to the ketotifen. This shows that olopatadine provided quicker relief from the symptoms than ketotifen. Similar findings were reported in another study where 42.5% - 62.5% patients receiving olopatadine showed improvement in the symptoms and signs at 30 minutes compared to 20% - 27.5% receiving ketotifen and 80% - 87.5% reduction by 7th day compared to 60% - 75%.[108] Two other studies have shown that olopatadine 0.1% was effective than ketotifen.[109, 110]

The other parameter assessed was quality of life which improved from the baseline in both groups but was similar between the groups (Table 6). In the Scoper et al study it was observed that patients receiving olopatadine 0.2% had significant improvement in quality of life.[111] In another study patients preferred olopatadine.[112]

10% patients receiving olopatadine and 18.3% ketotifen reported adverse reaction, most common being headache followed by burning sensation in the eyes. In a study including 100 patients it was observed that 98% receiving ketotifen reported burning

sensation in the eyes.[112] Stinging sensation in eyes was observed in 22.5% patients receiving ketotifen.[108] A study monitoring adverse drug reactions (ADRs) to different drugs, found that olopatadine 0.1% manifested with 4.65% ADRs and ketotifen 7.35%.[113] In our study 4 and 8 patients in olopatadine and ketotifen respectively reported headache while the incidence of burning sensation was 2 and 3 (Table 7).

In this study olopatadine provided quicker relief of symptoms and signs that is, by 4 days, the cost was 84 rupees as the patients utilized only a single vial, whereas ketotifen took longer time that is, 15 days and some patients required two vials therefore the cost ranged from 57 to 114 rupees.

CONCLUSION

CONCLUSION

- Allergic conjunctivitis (AC) is an atopic ocular disorder caused by an IgE-mediated immune or immediate hypersensitivity mechanism, associated with itching, redness, tearing, pain, burning and foreign body sensation in the eyes.
- The treatment of AC includes administration of antihistamines, mast cell stabilizers, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.
- Topical medications used are olopatadine hydrochloride 0.1% and ketotifen fumarate 0.025%.
- The baseline individual, total AC and quality of life (QOL) score were comparable between the groups.
- There was a significant reduction in the individual, total AC and QOL score by the 4^{th} and 15^{th} day compared to baseline in both the groups.
- By 4th day the itching, tearing, hyperemia and total AC scores reduced significantly (p=0.001) and by 15th day there was significant reduction (p=0.001) in the above scores and also papillae in patients receiving olopatadine compared to ketotifen, QOL was comparable between the groups.
- There were fewer adverse effects reported by the patients receiving olopatadine.
- Only one vial of olopatadine was used whereas some patients required two vials of ketotifen.
- The cost of the olopatadine was 84 rupees per patients and for ketotifen it ranged from 57-114 rupees per patients.
- Patients receiving olopatadine had quicker relief of symptoms of AC and was safe compared to ketotifen.

SUMMARY

SUMMARY

Allergic eye disease is a common ocular atopic disorder caused by the inflammation of the conjunctiva. In this study 120 patients with allergic conjunctivitis (AC) were randomized to receive either olopatadine HCl 0.1% two drops twice daily or ketotifen fumarate 0.025% two drops four times a day. They were assessed for improvement in their symptoms and signs (AC score) and quality of life (QOL) score on the 4^{th}, 15^{th} and the 30^{th} day. Adverse effects were also noted and cost of the treatment was analyzed.

There were 67 males and 53 females, with mean age of 36.35 ± 11 years. 42 and 34 patients in respective groups had pervious history of AC and symptoms aggravated with seasonal variation or in the presence of dust. The baseline total AC and QOL scores were comparable between groups. Patients receiving either olopatadine or ketotifen have shown significant reduction (p=0.001) in the individual, total AC and quality of life scores by 4^{th} and 15^{th} day compared to baseline. By 4th day the itching, tearing, hyperemia and total AC scores reduced significantly (p=0.001) and by 15th day there was significant reduction (p=0.001) in the above scores and also papillae in patients receiving olopatadine compared to ketotifen, QOL was comparable between the groups. A total of 10% and 18.3% reported either headache or burning sensation in eyes with olopatadine and ketotifen respectively. The cost of one olopatadine HCl vial was 84 rupees per patient whereas for ketotifen fumarate it ranged from 57 to 114 rupees.

Thus in our study we observed that olopatadine provided quicker relief of symptoms compared to ketotifen with fewer adverse effects.

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ANNEXURES

PROFORMA

OP No.: Date:

Serial No.:

1. Name: 2. Age: 3. Gender:
4. Occupation: 5. Educational Status:
6. Address with Phone no.:

7. Complaints:
   Duration:
   Symptoms:
   Aggravating Factors:
   Seasonal Variation:

8. Family History of Asthma:
9. Personal History: smoking/alcohol/drug intake/DM/HTN/Bronchial Asthma:
10. Past history of same complaints and treatment if taken:
12. History of contact with patient of AC:

13. General Physical Examination:
    CVS:
    RS:
    CNS:
    PA:

14. Examination of the Eye:
    Head Posture:
    Ocular Posture: Hirschberg's Reflex
    Facial Symmetry:
    Eye Lids:
    Conjunctiva:
    Cornea:
    Iris:
    Pupil:
    Lens:
    Vision:
    IOT:
    Extra Ocular Movements:
    Refraction:
    Fundus:

15. Diagnosis:
16. Treatment with dosage:
17. QOL Questionnaire:

FOLLOW UP VISITS

	Baseline					Day 4					Day 15					Day 30				
Date																				
Score	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Compliance																				
Itching																				
Tearing																				
Redness																				
Eyelids Swelling																				
Chemosis																				
Papillae																				
Adverse Reactions																				

Day 30: QOL Questionnaire.

QUALITY OF LIFE QUESTIONNAIRE

Activities

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15
1.																					
2.																					

Sleep

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15
3.Difficulty getting sleep																					
4. Lack of good night's Sleep																					

Practical problems

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15
5.Inconvenience of having to carry tissue or handkerchief																					
6. Need to rub nose or eyes																					
7.Need to blow nose repeatedly																					

Nasal Symptoms

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15
8.Running Nose																					
9. Post nasal Drip																					

Eye Symptoms

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15
10.Itchy Eyes																					
11.Watey Eyes																					
12.Sore Eyes																					
13.Swollen eyes																					

Emotional

	None of The Time			Hardly Any Time At All			A Small Part Of The Time			Some Part Of The Time			A Good Part Of The Time			Most Of The Time			All Of The Time		
	0			1			2			3			4			5			6		
Day / Act.	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15	0	7	15
14. Irritable																					
15.Embarrassed by your symptom																					

MASTER CHART

KEY TO MASTER CHART

S. No.	- Serial number
Gen	- 1- Male
	2- Female
OP No.	- Hospital Outpatient number
History of AC	- Previous history of allergic conjunctivitis 1- Yes, 2- No
Aggravating factors	- 1- Summe, 2- Dust, 3- None
AC Score 0, 4, 15, 30	- Allergic conjunctivitis score on Day 0, 4 15 and 30
Itching 0, 4, 15, 30	- Itch score on Day 0, 4 15 and 30
Tearing 0, 4, 15, 30	- Tearing score on Day 0, 4 15 and 30
Redness 0, 4, 15, 30	- Hyperemia score on Day 0, 4 15 and 30
Eyelid swelling 0, 4, 15, 30	- Eyelid swelling score on Day 0, 4 15 and 30
Chemosis 0, 4, 15, 30	- Chemosis score on Day 0, 4 15 and 30
Papillae 0, 4, 15, 30	- Papillae score on Day 0, 4 15 and 30
QOL Score 0, 4, 15	- Quality of life score on Day 0, 4 and 15
ADR	- Adverse drug reaction 1- No, 2- Yes
Reaction	- 1- None
	2- Headache
	3- Burning sensation in the eyes
Loss	- Loss to follow up 0- No, 1- Yes
Group	- Study group 1- Olopatadine HCl 0.1%
	2- Ketotifen fumarate 0.025%

S.No	OP No.	Date	Name	Age	Gen	Occupation	History of AC	Aggravating factors	AC Score				Itching				Tearing				Redness				Eyelid Swelling				Chemosis				Papillae				QOL Score			ADR	Reactions	Loss	Group
									0	4	15	30	0	4	15	30	0	4	15	30	0	4	15	30	0	4	15	30	0	4	15	30	0	4	15	30	0	7	15				
1	592503	03-02-12	Faizunissa	62	2	Housewife	1	1	9	4	0	0	3	1	0	0	3	1	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	42	7	0	1	1	0	1
2	708836	03-07-12	Khadeer	20	1	Engineer	1	1	10	5	0	0	3	2	0	0	3	1	0	0	3	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	38	8	0	1	1	0	1
3	37189	13/3/2012	Srinivas	25	1	Electrician	1	1	10	1	0	0	4	1	0	0	3	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	45	10	0	1	1	0	1
4	37275	13/3/2012	Manjunath	24	1	Electrician	1	1	9	8	0	0	3	3	0	0	3	2	0	0	2	2	0	0	0	0	0	0	0	0	0	0	1	1	0	0	36	14	0	1	1	0	1
5	781705	15/3/2012	Shahina Taj	35	2	Housewife	1	2	10	4	0	0	4	2	0	0	2	1	0	0	3	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	34	17	0	1	1	0	1
6	38165	16/3/2012	Wasim Akram	11	1	Student	1	1	10	4	0	0	4	2	0	0	3	1	0	0	2	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	33	12	0	1	1	0	1
7	3395	20/3/2012	Gousepeer	17	2	Student	2	3	12	8	0	0	4	3	0	0	3	2	0	0	3	2	0	0	1	0	0	0	0	0	0	0	1	1	0	0	25	19	0	1	1	0	1
8	788477	22/3/2012	Kavya Sai	20	2	Student	1	2	11	7	0	0	4	2	0	0	3	2	0	0	3	2	0	0	0	0	0	0	0	0	0	0	1	1	0	0	23	21	0	1	1	0	1
9	41058	27/3/2012	Munireddy	39	1	Attender	1	2	12	9	0	0	4	3	0	0	3	3	0	0	3	2	0	0	1	0	0	0	0	0	0	0	1	1	0	0	32	14	0	1	1	0	1
10	46796	13/4/2012	Pramod Kumar	11	1	Student	1	2	9	3	0	0	3	2	0	0	3	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	27	9	0	1	1	0	1
11	46800	13/4/2012	Ajay Kumar	14	1	Student	2	3	10	4	0	0	3	2	0	0	3	1	0	0	3	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	27	17	0	1	1	0	1
12	46836	13/4/2012	Anjanappa	30	1	Constructor	2	3	10	3	0	0	4	2	0	0	2	1	0	0	3	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	25	12	0	1	1	0	1
13	48019	17/4/2012	Yuvraj	25	1	Carpenter	1	1	10	3	0	0	3	1	0	0	3	1	0	0	3	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	24	19	0	1	1	0	1
14	772670	05-03-12	Mithila R	25	2	Student	2	3	11	7	0	0	4	2	0	0	3	2	0	0	3	2	0	0	0	0	0	0	0	0	0	0	1	1	0	0	23	21	0	1	1	0	1
15	5897	29/5/2012	Kempanna	50	1	Agriculturist	2	3	10	1	0	0	4	1	0	0	3	1	0	0	2	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	19	13	0	2	2	0	1
16	3902	06-05-12	Krithin M	12	1	Student	1	1	12	6	0	0	4	2	0	0	3	1	0	0	3	2	0	0	0	0	0	0	0	0	0	0	1	1	0	0	27	19	0	1	1	0	1
17	732305	13/6/2012	Ravindrappa	49	1	Mechanic	1	1	10	7	0	0	4	2	0	0	3	2	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	48	22	0	1	1	0	1
18	730763	22/6/2012	Kamalakar	38	1	Clerk	1	1	11	6	0	0	4	3	0	0	3	1	0	0	3	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	33	8	0	1	1	1	1
19	730773	07-12-12	Goppamma	44	2	Housewife	1	2	12	5	0	0	4	3	0	0	3	1	0	0	3	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	48	10	0	1	1	0	1
20	769415	19/7/2012	Kalavathi	36	2	Housewife	1	2	11	6	0	0	4	3	0	0	3	1	0	0	3	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	48	14	0	1	1	0	1
21	757552	23/7/2012	Sumiya	10	2	Student	1	1	12	6	0	0	4	2	0	0	3	2	0	0	3	1	0	0	1	0	0	0	0	0	0	0	1	1	0	0	27	13	0	2	2	0	1
22	747474	08-08-12	Vasanthamma	47	2	Housewife	1	1	12	7	0	0	4	2	0	0	3	2	0	0	3	2	0	0	1	0	0	0	0	0	0	0	1	1	0	0	53	12	0	1	1	0	1
23	747423	17/8/2012	Rathnamma	46	2	Housewife	2	3	11	6	0	0	4	3	0	0	3	1	0	0	3	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	54	19	0	1	1	0	1
24	747460	21/8/2012	Dheeraj	33	1	Mechanic	1	1	12	6	0	0	4	3	0	0	3	2	0	0	3	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	50	21	0	1	1	0	1
25	747376	14/9/2012	Arvind	36	1	Shopkeeper	1	1	10	5	0	0	4	2	0	0	3	1	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	42	14	0	1	1	1	1
26	747404	24/9/2012	Dayanand	55	1	Business	1	1	11	5	0	0	4	2	0	0	3	1	0	0	3	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	44	9	0	1	1	0	1
27	746974	10-03-12	Nagendra	28	1	Carpenter	2	3	10	7	0	0	4	3	0	0	3	2	0	0	3	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	50	10	0	1	1	0	1
28	746889	18/10/2012	Anandappa	44	1	Mechanic	2	3	11	5	0	0	4	2	0	0	3	1	0	0	3	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	38	7	0	1	1	0	1
29	749920	11-07-12	Ramareddy	46	1	Business	1	2	12	3	0	0	4	2	0	0	3	0	0	0	3	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	45	8	0	1	1	0	1
30	764422	21/11/2012	Narayanamma	28	2	Housewife	2	3	10	8	0	0	4	3	0	0	3	2	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	27	16	0	1	1	0	1
31	765467	12-05-12	Naseer Ahmed	38	1	Accountant	2	3	12	6	0	0	4	3	0	0	3	2	0	0	3	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	40	9	0	1	1	0	1
32	765437	01-03-13	Ananth Reddy	39	1	Driver	1	1	10	5	0	0	4	2	0	0	3	1	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	43	17	0	2	2	0	1
33	765401	16/1/2013	Nanjamma	44	2	Housewife	1	1	9	3	0	0	4	1	0	0	2	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	29	10	0	2	2	0	1
34	762825	22/1/2013	Bhagya	30	2	Teacher	1	1	10	4	0	0	4	2	0	0	3	1	0	0	2	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	34	13	0	1	1	0	1
35	764816	26/1/2013	Ramoji Rao	39	1	Shopkeeper	1	1	9	4	0	0	4	2	0	0	2	1	0	0	2	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	39	19	0	1	1	0	1
36	764791	30/1/2013	Lokesh	36	1	Accountant	1	1	12	0	0	0	4	0	0	0	3	0	0	0	3	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	40	0	0	1	1	1	1
37	770051	02-04-13	Krishnamurthy	42	1	Agriculturist	1	1	11	7	0	0	4	3	0	0	3	2	0	0	3	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	31	11	0	1	1	0	1
38	710035	02-09-13	Hemalatha	37	2	Teacher	1	1	11	7	0	0	4	3	0	0	3	2	0	0	3	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	27	8	0	1	1	0	1
39	771137	13/2/2013	Shamlamma	46	2	Housewife	2	3	11	7	0	0	4	2	0	0	3	2	0	0	3	2	0	0	0	0	0	0	0	0	0	0	1	1	0	0	36	13	0	1	1	0	1
40	771133	18/2/2013	Badrinath	39	1	Driver	1	2	10	3	0	0	4	2	0	0	3	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	26	16	0	1	1	0	1
41	731049	22/2/2013	Santosh	45	1	Hotel Cook	1	2	12	5	0	0	4	2	0	0	3	2	0	0	3	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	42	18	0	1	1	0	1
42	771705	26/2/2013	Siddhartha	36	1	Lawyer	1	2	9	3	0	0	4	1	0	0	2	1	0	0	2	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	37	20	0	1	1	0	1
43	741639	03-01-13	Narendra	59	1	Engineer	2	3	10	6	0	0	4	3	0	0	3	2	0	0	2	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	33	7	0	1	1	0	1
44	772452	03-05-13	Amrutha	28	2	Nurse	2	3	12	3	0	0	4	1	0	0	3	1	0	0	3	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	41	13	0	1	1	0	1
45	772430	03-09-13	Anandbabu	42	2	Business	1	2	10	5	0	0	4	2	0	0	3	1	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	46	16	0	1	1	0	1
46	739370	13/3/2013	Dasappa	40	1	Driver	2	3	11	7	0	0	4	3	0	0	3	2	0	0	3	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	28	12	0	1	1	0	1
47	773178	18/3/2013	Basappa	39	1	Farmer	2	3	10	4	0	0	4	1	0	0	3	1	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	30	18	0	1	1	0	1
48	762825	22/3/2013	Bhavya	36	2	Teacher	1	1	12	5	0	0	4	2	0	0	3	1	0	0	3	1	0	0	1	0	0	0	0	0	0	0	1	1	0	0	42	11	0	2	3	0	1
49	764788	26/3/2013	Chowdamma	48	2	Housewife	1	2	9	5	0	0	4	2	0	0	2	1	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	38	19	0	1	1	0	1
50	748270	30/3/2013	Nagamma	54	2	Labourer	1	1	10	0	0	0	4	0	0	0	2	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	26	0	0	1	1	1	1
51	774368	04-03-13	Mallikarjun	38	2	Beautician	1	2	12	2	0	0	4	1	0	0	3	0	0	0	3	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	28	12	0	1	1	0	1
52	775077	04-08-13	Pavan Reddy	35	1	Shopkeeper	1	1	10	6	0	0	4	3	0	0	3	1	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	34	7	0	1	1	0	1
53	775104	04-12-13	Manohar	35	1	Business	1	2	9	4	0	0	4	1	0	0	2	1	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	41	15	0	1	1	0	1
54	761036	16/4/2013	Ganesh	45	1	Farmer	1	2	11	2	0	0	4	1	0	0	3	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	38	11	0	2	3	0	1
55	760972	20/4/2013	Kamal Khan	39	1	Accountant	2	3	9	6	0	0	4	2	0	0	2	2	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	26	9	0	1	1	0	1
56	733367	24/4/2013	Bhavini	46	2	Nurse	1	2	11	3	0	0	4	2	0	0	3	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	33	18	0	1	1	0	1
57	730938	28/4/2013	Gangappa	40	1	Agriculturist	1	1	9	6	0	0	4	3	0	0	2	1	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	46	10	0	1	1	0	1
58	730969	05-02-13	Paratha Sarathi	36	1	Mechanic	1	2	11	3	0	0	4	2	0	0	3	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	29	12	0	1	1	0	1
59	734717	05-06-13	Pavan Reddy	37	1	Engineer	2	3	12	0	0	0	4	0	0	0	3	0	0	0	3	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	36	0	0	1	1	1	1
60	752915	05-10-13	Ramakishnappa	53	1	Electrician	2	3	10	3	0	0	4	1	0	0	2	0	0	0	3	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	38	15	0	1	1	0	1