UNIVERSITY OF KHARTOUM

Faculty of Medicine

POSTGRADUATE MEDICAL STUDIES BOARD

Effect of Sodium Cromoglycate in Sudanese patients with Vernal Keratoconjunctivitis

By

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بسم الله الرحمن الرحيم

(رب اوزعنى ان اشكـر نعمتك التى انعمــت علىّ
و على والدى وان اعمـل صالحـاً ترضـاهـ)

صـدق الله العظـيم
الاحقاف (15)

Dedication

To My parents

My teachers

& My patients

Amira

CONTENTS

ACKNOWLEDGEMENT

I would like to thank my supervisor Dr. Abdul Rahman Diab who spent much of his valuable time listening and discussing with me every possible detail in the study. I am pleased to have the honour of learning and searching under his direct guidance.

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I will never overlook my magnificent family who provided me with the environment for studying. At last, I will remain grateful to all my beloved patients for their understanding and cooperation.

Thanks to Allah without whom nothing can be done.

ABSTRACT

Vernal keratoconjunctivitis (VKC) is an allergic condition which predominantly affects male children and young adults. VKC victims may suffer from symptoms throughout the year, but the intensity of signs and symptoms increases during the hot seasons. Mast cells appear to play an important role in the pathogenesis of VKC.

Objective:

This study aims to evaluate from a clinical point of view the role of sodium cromoglycate in the treatment of VKC.

Methods:

In a single masked interventional study, done in Makkah Eye Complex in Khartoum state during the period Jan – June 2004, 97 patients with vernal keratoconjunctivitis were included in this study, 68 patients were the study group using sodium cromoglycate eye drops and 29 patients were the control group using tears naturale as a placebo.

A questionnaire designed containing all necessary information was completed and full ocular examination for each patient was performed. Signs and symptoms were graded and

recorded in three stages: stage 1(baseline examination), stage 2 (after 2 weeks) and stage 3 (after 4 weeks). Treatments were given to the patients as follows: first two weeks steroids plus sodium cromoglycate for the study group and steroid plus placebo for the control group. At the end of the first 2 weeks steroid stopped and treatment continued with sodium cromoglycate for the study group and placebo for the control group for 4 weeks.

Results:

Itching and hyperaemia were the main presenting symptom and sign of VKC. In the first follow up there was improvement in symptoms and signs of both study and control groups and this was attributed to the anti-inflammatory effect of steroid.

In the second follow up there was a significant improvement in the symptoms and signs among the study group and this was attributed to the mast cell stabilization effect of sodium cromoglycate while in the control group the improvement was not significant, and some symptoms and signs were getting worse.

Conclusion:

Sodium cromoglycate is effective as a prophylactic drug in the treatment of VKC.

ملخص الاطروحة

الرمد الربيعي هو حالة حساسية بالعين ، يصيب الاطفال و المراهقين ونسبة حدوثه لدى الذكور اعلى من الاناث ويلاحظ أن المصاب بالرمد الربيعي قد يعاني من الاعراض طوال السنه ولكن حدة الأعراض تزداد خلال موسم الصيف. وعن كيفية حدوث المرض تبين من خلال الدراسات والبحوث ان ما يعرف بالخلايا البدينة تلعب دوراً أساسياً في أمراضية الرمد الربيعي.

الهدف :

دف الدراسة الى تقييم دور كروموجلايكات الصوديوم في معالجة الرمد الربيعي وذلك من خلال رؤية إكلينيكية.

الطريقه :

دراسه تدخليه احاديه الحجب اجريت بمجمع مكه لطب العيون بولاية الخرطوم خلال الفتره من يناير وحتى يونيو 2004. سبعه وتسعون مريضاً يعانون من الرمد الربيعي ضمنوا في هذه الدر اسه بحيث مثل ثمانيه وستون مريضاً منهم مجموعة الدراسة فتم اعطاؤهم كروموجلايكات الصوديوم قطرة للعين بينما مثل تسعة وعشرون مريضاً مجموعة التحكم و تم إعطاؤهم الدموع الصناعيه كبديل لكروموجلايكات الصوديوم وليس له تأثير علاجى فى حالات الرمد الربيعى.

تم تصميم استبيان يحتوي على كل المعلومات الضروريه المطلوبة للدراسة كما تم اجراء كشف كامل للعينين لكل مريض.ومن ثم تم تدريج وتسجيل أعراض و علامات المرض طبقاً لشد ا على ثلاثه مراحل:-

المرحله الاولى :الفحص الأولي ويمثل الخط القاعدي.

المرحله الثانيه : عند المراجعه بعد اسبوعين.

المرحله الثالثه : عند المراجعه بعد اربعه اسابيع.

اعطى العلاج للمرضى الذين شملتهم الدراسة على النحو التالي:

1. مجموعة الدراسه اعطيت سترويد بالاضافه الى كروموجلايكات الصوديوم.
2. مجموعه التحكم اعطيت سترويد بالاضافه الى الدموع الصناعيه.
3. عند ايه الاسبوع الثاني تم ايقاف المعالجة بالاسترويد من كلتا المجموعتين واستمرت المعالجة لمجموعة الدراسه بكروموجلايكات الصوديوم فقط بينما استمرت لمجموعة التحكم بالدموع الصناعيه فقط.

تم رصد النتائج بنهايه الاسبوع الرابع .

النتائج :

1. مثلت الحكه العرض الأساسي المسبب لحضور المريض للمستشفى بينما مثل الاحمرارالعلامة السائدة عند الكشف على المريض.
2. في المراجعه الاولى حدث تحسن ملحوظ في الاعراض والعلامات للمجموعتين مجموعة الدراسه و مجموعه التحكم .نتج هذا التحسن غالبا من تأثير الاسترويد المضاد للالتهاب.
3. في المراجعه الثانيه حدث تحسن ملحوظ في الاعراض والعلامات بالنسبه لموعه الدراسه ويعزى ذلك غالبا لتاثير كروموجلايكات الصوديوم المثبت للخلايا البدينة، اما بالنسبه لموعه التحكم فان التحسن لم يكن ملموساً بل ساءت بعض الاعراض والعلامات.

الخلاصه :

كروموجلايكات الصوديوم يعتبر دواءً وقائياً فعالاً في معالجة الرمد الربيعي.

List of abbreviations

VKC	Vernal Keratoconjunctivitis
TCRs	T-cell receptors
MHC	Major histocompatibility complex
Ig	Immunoglobulin
NK	Natural killer
MCT	Tryptase mast cells
MCTC	Tryptase-chymase mast cells
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
EMBP	Eosinophil granule major basic protein
PG	Prostaglandins
IL	Interleukin
F.B	Foreign body
AKC	A topic Keratoconjunctivitis
GPC	Giant papillary conjunctivitis
RAST	Radioallergosorbent test
SRS-A	Slow reacting substance of anaphylaxis
DSCG	Disodium cromoglycate
NSAIDs	Non steroidal anti inflammatory drugs

PLA	Platelet activating factor
PGE1	Prostaglandins E1
PGE2	Prostaglandins E2
PGF2	Prostaglandins F2
PGD2	Prostaglandins D2
PGF	Prostaglandins F
IgM	Immunoglobulin M
IgG	Immunoglobulin G
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgD	Immunoglobulin D

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CHAPTER ONE

1.1 INTRODUCTION

Ocular allergy affects 15-20% world-wide population. Ninety percent of allergies have ocular symptoms. Ninety three percent of patients with hay fever have ocular components. Vernal keratoconjunctivitis is a disabling disease of children and young adults. It is characterized by itching, redness, tearing, foreign body sensation, photophobia and thick mucoid discharge.

Patients of VKC present with conjunctival and corneal findings. The conjunctival signs consist of hyperaemia, oedema, papillary hypertrophy and giant papillae. The limbal signs consist of infiltration with tissue hyperplasia, fibrovascular growth, limbal vascularisation and Trantas' dots.

The cornea in VKC may show punctate staining, corneal plaque and corneal scars.

The reduction in vision is caused either by the sequelae of the disease itself (corneal plaque and scars) or as a complication of treatment. It is, therefore, conceded that continuous research for new drugs that are safe and effective and steroid sparing is highly desirable.

Mast cell stabilisers, such as sodium cromoglycate, carry very few side effects, but patients need to receive treatment for several days before the expected exposure to allergen. Maintenance with these topical mast cell stabilizing agents during the seasonal period of activity generally keeps the symptoms in check.

Sodium cromoglycate inhibits the degranulation of sensitized mast cells that occurs after exposure to specific antigen. Through this inhibition sodium cromoglycate prevents subsequent release of chemical mediators such as histamine that cause hypersensitivity reactions. Sodium cromoglycate is used in allergic ocular disorders e.g. allergic conjunctivitis, GPC and VKC. It is also used as a prophylaxis in asthma, chronic bronchitis, allergic rhinitis and food allergy.

In Sudan which has a dry dusty hot weather, VKC occurrs through out the year. This is what was found by Dr. Mohammed Nour Hassan in a study done in 1984. He found that the incidence increases during summer from April to August and this is related directly to the weather.

1.2 LITERATURE REVIEW

1.2.1 GENERAL DESCRIPTION AND FUNCTIONS:

1.2.1.1Conjunctiva:

The conjunctiva is a thin translucent mucous membrane which joins the eye ball to the eyelids [1, 2]. It forms a smooth, flexible protective sac which covers the pericorneal surface of the anterior portion of the eye and lines the posterior surface of the eyelids [1, 3].

Although conjunctiva is continuous, it is conveniently described in three regions palpebral, bulber and fornical [1]. The palpebral conjunctiva extends from the mucocutaneous junction at the lid margin to the upper and lower margins of the tarsal plates.

In the fornix, the conjunctiva is loosely attached to the orbital septum. The fornical conjunctiva extends temporally behind the lateral canthus and nasally to the semilunar fold. Ducts of the lacrimal gland open into the temporal portion of the upper fornix; those of the accessory glands of Krause and Wolfring open into the upper and lower fornices.

The bulbar conjunctiva is loosely adherent to the sclera and extends from the limbus to the fornical area [3].

Histology: Microscopic Structure:

As a mucous membrane, conjunctiva has an epithelium and sub-mucosal lamina propria [(1)].

Epithelium: stratified columnar cells consisting of two to five layers. At the limbus there is a change to stratified squamous non keratinized epithelium.

Conjunctival sub-mucosa: consists of fine delicate connective tissue which ends at the edges of the cornea [(2)].

Blood Supply:

The arterial supply of conjunctiva arises from the two marginal and peripheral palpebral arches of the eye lid. The veins are more numerous than the arteries; they accompany the arteries and drain into palpebral veins or directly into the superior or inferior ophthalmic veins [(2)].

Nerve Supply:

The sensory innervations of the bulbar conjunctiva are from the long ciliary nerves. Innervations of superior palpebral conjunctiva and the superior fornix are from the frontal and lacrimal nerves. Innervations of inferior palpebral conjunctiva and the inferior fornix is from lacrimal and infraorbital nerves [(2)].

Function:

The conjunctiva secretes mucus, serves as a repository for lacrimal gland and eyelid margin secretions, and aids their transportation to the nasolacrimal outflow passages. The intact conjunctival epithelial surface and its secretions form a barrier to the entrance of exogenous infections and foreign particles. Blinking assists in lubricating and moistening the cornea through distribution of the tear film, and the smooth palpebral surface permits movement of the eyelid over the cornea without damage to the corneal surface [(3)].

1.2.1.2 Cornea:

The cornea forms the anterior one sixth of the circumference of the outer coat of the eye. The adult cornea has an average diameter of approximately 10.6 mm vertically and 11.7 mm horizontally [(1)]. The anterior and posterior surfaces are parallel to each other in the central 4-mm, spherically shaped "optical zone," where the cornea averages 0.52 mm in thickness. There is a slight flattening of the corneal curvature peripherally. In this area, the anterior and posterior corneal surfaces are no longer parallel, and the corneal thickness increases to an average of 0.65 mm.

The cornea is divisible into five distinct layers:

Epithelium:

Centrally, the epithelium is composed of five to six layers of stratified squamous epithelium. Towards the periphery, the number of cell layers increases to eight to ten. The basal layer of epithelium consists of pale-staining, tall polygonal cells containing oval nuclei oriented at a right angle to the surface of the cornea.

Bowman's Layer:

Bowman's layer is a uniformly thick acellular structure that underlies the basement membrane of the epithelium. Bowman's layer is believed to represent a modified layer of the anterior stroma and is composed of randomly oriented, loosely packed, small collagen fibrils surrounded by mucoprotein ground substance.

Substantia Propria:

The substantia propria or stroma, forms approximately 90% of the thickness of the cornea. It is a vascular and consists of collagenous lamellae interspersed with cells (keratocytes) and ground substance. The lamellae are broad bands of interlacing collagenous fibrils extending

over the entire width of the cornea and arranged almost parallel to one another and to its surface.

Descemet's Membrane:

Descemet's membrane lies on the posterior aspect of the stroma. It is a true basement membrane, being formed by corneal endothelial cells. At its periphery, Descemet's membrane terminates at the junction between corneal and trabecular endothelium. Descemet's membrane is acellular and is faintly eosinophilic staining.

Endothelium:

The endothelium is a single layer of polygonal cells that extends over the inner surface of Descemet's membrane [3].

Nerve Supply:

The cornea is richly supplied with unmyelinated nerves derived from the ciliary nerves, which are end branches of the ophthalmic division of the fifth cranial nerve. The nerves are unmyelinated and wrapped by Schwann cells in the stroma but not in the corneal epithelium.

Blood Supply:

The limbus contains numerous arterial channels, derived from the anterior conjunctival and ciliary vessels, as well as venous channels from the region of the ciliary body

(anterior ciliary veins). Their major function is to nourish the conjunctiva, episclera, and the sclera in the region of Schlemm's canal. The peripheral corneal stroma undoubtedly derives a portion of its nourishment from these vessels as well. In pathologic states, these vessels serve as a source of subepithelial and stromal neovascularization [1,3].

The cornea serves to protect the more delicate structures of the anterior segment of the eye from injury. It is also an important component of the refractive system of the eye. Light incident on the eye is first sharply converged at the outer surface of the cornea, where there is an abrupt transition in the index of refraction from air (index 1.0) to the precorneal tear film (Index 1.37). Minor changes in corneal curvature, therefore, can cause relatively large changes in refractive power [3].

1.2.1.3 Tear film:

This consists of three layers:

- Outer lipid layer; secreted by Meibomian glands Its function is to retard evaporation of the aqueous layer, lower surface tension of the tear film and lubricate the eye lids as they pass over the globe.

- Middle aqueous layer; secreted by lacrimal glands and consist of proteins, electrolytes and water. Its function is to supply atmospheric oxygen, antibacterial function due to the presence of tear proteins such as IgA, lysozyme and lactoferrin. To abolish any minute irregularities of the anterior corneal surface, to wash away debris and noxious stimuli and allow the passage of leucocytes after injury.
- Inner mucin layer; secreted by goblet cells, crypts of Henle and glands of Manz .Its function is wetting the cornea by converting the corneal epithelium from a hydrophobic to hydrophilic state [(4)].

1.2.2 IMMUNOLOGY

1.2.2.1 Definition:

Immunity is defined as a host system's response to molecules identified as foreign. This concept would then encompass immune regulation, with "appropriate" responses resulting in beneficial outcomes for the host (i.e., control of infection, tumor surveillance) and "inappropriate" responses resulting in deleterious outcomes (i.e., autoimmune disease, immediate hypersensitivity) [5].

A specific immune response involves the interaction of effector mechanisms such as complement, phagocytes, inflammatory cells, and cytokines. However, since these responses are not directed against the inciting agent only, usually injury to the surrounding host tissue occurs as well. Under normal conditions, due to the self-limiting nature of immune responses, these injurious reactions are minimal and dampened when the foreign antigen is eliminated. In addition, due to tolerance to autoantigens, immune responses to autologous tissues do not usually occur. In some cases, however, when a specific immune response is not appropriately controlled, a phenomenon termed hypersensitivity ensues [6].

1.2.2.2 Innate versus acquired immunity:

The immune response has classically been divided into innate and acquired immunity. Innate immunity represents the first line of defense for the individual. The chief components of innate immunity are the mononuclear phagocyte system, including cytokines, complements proteins and physiochemical barriers.

Acquired immunity is defined by the specific recognition of foreign molecules by lymphocytes and their products. Before exposure to antigens, antigen-specific lymphocytes develop, that are capable of recognition and response to foreign molecules. This represents the primary response. Activation of lymphocytes results in immunologic memory with the resultant capacity for dramatic amplification of specific and nonspecific effector function on re-exposure to the offending molecules, more commonly known as the secondary response. The immune system is capable of recognizing more than 109 antigenic determinants. This remarkably large repertoire results from variability at the antigen-binding sites of immunoglobulins and T-cell receptors (TCRs) [(5)].

Acquired immunity can be further subdivided into humoral and cell-mediated immunity. Humoral immunity is primarily mediated by immunoglobulins, the products of B lymphocytes, either in secreted form or as membrane-bound cell surface receptors. T lymphocytes are primarily responsible for cell-mediated immunity. Recognize, however, that the interaction between B and T cells is crucial in both forms of immunity [5].

Antigens:

Antigens are molecules capable of specifically binding to lymphocyte receptors. More precisely, immunogens are those antigens whose binding evokes an immune response. Whereas immunoglobulins are capable of binding soluble antigens, TCRs bind only processed peptides presented in the context of specific cell surface proteins, collectively called the major histocompatibility complex (MHC) gene products[5].

1.2.2.3 Physiochemical Barriers:

In the eye, the conjunctiva and the tear fluid layer provide the primary barrier against environmental aeroallergens, chemicals, and infectious agents [5]. The conjunctiva has a rich supply of immunoglobulins. Extracellular IgG, IgA, IgM

and IgE all of which have been found in the conjunctiva's substantia propria, may come from the rich vascular supply, the abundant plasma cells, the tear film, the lacrimal gland, or more likely, from all four sources[7].

1.2.2.4 Lymphocytes:

Lymphocytes are the cells responsible for the specificity of immune recognition and for coordination of the immune response. They are divided into three classes: T-cells lymphocytes, B-cells lymphocytes and natural killer (NK) cells. T-cells and B-cells are morphologically indistinguishable, small 8 to 10 µm in diameter lymphocytes with large nuclei. They are functionally distinct and are easily differentiated by the cell surface proteins they express: T-cells with CD3, CD4 and CD8 and B-cells with CD-19 surface markers.

B-cells are primarily responsible for humoral immunity and are the exclusive producers of immunoglobulins thus playing a vital role in the recognition and elimination of foreign antigen. Mature B cells can be divided into memory cells for the development of a rapid secondary response and plasma cells, which are totally committed to produce a single protein, an immunoglobulin. Plasma cells are

terminally differentiated producers of large amounts of antibody. B cells also interact closely with helper T cells through cell surface proteins such as CD40 and class II MHC and their complementary ligands.

However, an antigen stimulates a polyclonal B-cell response, which results in many plasma cells and immunoglobulin production of several classes or isotypes [5].

Mast cells can be divided into two types based on their expression of secretory granules: tryptase mast cells (MCT) and tryptase-chymase mast cells (MCTC). The predominant form of mast cell found in the normal conjunctiva is MCTC; however, there is a noticeable increase in the MCT type in chronic conjunctival inflammatory conditions. It is estimated that more than 50 million mast cells are present in the conjunctiva.

Mast cells and basophils are activated by the cross-linking of FceRI molecules on their surface after the binding of multivalent antigen to sufficient IgE. Activated mast cells release their preformed mediators in a regulated fashion and then synthesize lipid-derived mediators of inflammation [5].

1.2.2.5 Mediators:

Mediators are biologically active chemical compounds contained within inflammatory cells. On release from the cell, mediators act in a specific manner and at a specific site to induce a component of the inflammatory or immunologic process.

The mast cell surface has as many as 500,000 immunoglobulin-E (IgE) receptors, 10% of which are occupied in vivo. The Fc portion of the IgE molecule, the portion attached to the mast cell membrane, changes as a result of IgE cross-linking with the offending allergen, activating a serine esterase. This leads to an intracellular biochemical cascade causing mast cell degranulation and the subsequent release of preformed mediators, including histamine, eosinophil chemotactic factor of anaphylaxis, high-molecular-weight neutrophil chemotactic factor, and platelet-activating factor. These mediators attract eosinophils and neutrophils, which restore homeostasis to the tissue. The signs and symptoms of an acute allergic reaction result from this intricate network of mediator interaction [(5)].

The inflammatory process is regulated internally by a negative feedback system. The interaction of histamine with mast cell surface histamine receptors elevates cyclic adenosine monophosphate (cAMP) concentrations, thereby "turning off" the mast cell. The second messengers, cAMP and cyclic guanosine monophosphate (cGMP), further control mediator release from mast cells and basophils. Increasing levels of cAMP block mediator release; increasing levels of cGMP stimulate mediator release. Beta-adrenergic receptor activation enhances cAMP levels; alpha-adrenergic receptor activation diminishes cAMP levels. Prostaglandins act by way of adenyl cyclase to increase cAMP levels. Phosphodiesterase degrades cAMP; thus, phosphodiesterase inhibitors can increase cAMP levels. Cholinergic stimulation results in increasing levels of cGMP and mediator release. Thus, allergic symptoms can be treated by increasing cAMP levels or decreasing cGMP levels. Pharmacologic modulation of these feedback mechanisms may provide a novel method for the treatment of allergic diseases [(5)].

Preformed Mediators:

Histamine:

It is an endogenous substance, widely distributed in mammalian tissue. It is stored in the secretory granules of tissue mast cells located primarily in connective tissue associated with blood vessels. Histamine is also found in platelets and in basophils. Re-exposure of sensitized individuals to an inciting antigen activates cell-bound IgE dimers, inducing mast cell and basophil degranulation and resulting in histamine release [5].

Histamine is the key mediator producing itching, redness and chemosis in allergic conjunctivitis [8, 9].

There are two histamine receptor sites important in allergic conjunctivitis: H1 (itch, burn, plus minimal vasodilation) and H2 (vasodilation). Histamine levels have been described in normal human tears (5 to 10 ng/ml). These levels were found to be consistently elevated in the tears of patients with active vernal keratoconjunctivitis (VKC; 16 ng/ml) [5].This elevation is probably the result of the extensive mast cell degranulation demonstrated in patients with VKC by light and electron microscopy. In addition, patients with VKC have four times as many mast cells in their conjunctiva

as normal individuals [10], and the location of these mast cells is more superficial than in the normal conjunctiva [11], such patients are, therefore, at greater risk for antigenic attack[5].

Tryptase:

Tryptase is a preformed, tetrameric serine endoprotease found in mast cells. It is stored in abundant quantities in its fully active form. Elevated levels of tryptase have been found in tears of patients after eye-rubbing. Tryptase is found elevated in patients with VKC even during the remission phase [12].

Tryptase has the ability to potentiate the effect of histamine, activate eosinophils and mast cells, and attract eosinophils and neutrophils. Mast cell stabilizers have been shown to reduce tryptase levels after allergen challenge [5].

Chymase:

Chymase is a serine endoprotease that is stored, preformed and fully active, in the TC mast cells. Unlike tryptase, chymase is inhibited by plasma proteinase inhibitors. The presence of chymase has not yet been demonstrated in the eye, although its presence is

suggested by the large number of conjunctival mast cells of the MCTC phenotype [5].

Eosinophil granule major basic protein:

Eosinophil granule major basic protein (EMBP) accounts for more than 50% of the eosinophil granule protein and 25% of the total cellular protein.

EMBP is a strongly cationic molecule with a molecular weight of 9,300 in humans. VKC is associated with marked mast cell degranulation and eosinophil infiltration, providing further evidence that eosinophils play a role in tissue damage.

Increased tear levels of both EMBP and Charcot-Leyden crystal protein have been detected in patients with VKC. It appears that both VKC and contact lens-associated giant papillary conjunctivitis are characterized by eosinophil degranulation with the release of EMBP and other cytotoxic granule proteins that may further stimulate mast cell degranulation. The release of EMBP, a powerful epithelial toxic compound, may account for keratitis and shield ulcers in VKC [5].

Oxidative products of Arachidonic acid metabolism:

Calcium-requiring PLA2 and phospholipase C are rapidly activated during an allergic reaction, releasing cholesteryl esters. Cell membrane phospholipids are metabolized by the cholesteryl ester, leading to the production of arachidonic acid. Arachidonic acid is metabolized by two major pathways (the cyclooxygenase pathway and the lipoxygenase pathway), and the resulting metabolites are active inflammatory mediators [5]. The addition of aspirin to the treatment regimen of patients with intractable VKC has produced dramatic improvement in conjunctival and episcleral redness, and resolution of keratitis and limbal infiltration [8, 13, 14] indicating that many of the signs and symptoms of VKC may be linked to products of the cyclooxygenase pathway[8].

Cyclooxygenase products:

The cyclooxygenase pathway leads to the production of prostaglandins and thromboxanes. The prostaglandins PGE1, PGE2, PGF2a, and PGD2 have all been isolated from ocular tissue and aqueous humor, but PGD2 is the main prostaglandin produced by human mast cells. It causes redness, chemosis, mucous discharge, and

eosinophil chemotaxis in the eye. PGE2 has been shown to increase blood flow independently and to synergize with histamine, bradykinin, and interleukin (IL)-1 to increase vascular permeability. Some evidence suggests that PGF may also be involved in allergic disease. Elevated tear levels of PGF have been detected in patients with VKC. Studies suggest that certain prostaglandins may also have anti-inflammatory actions. Thus, prostaglandins may also play a role in the negative feedback system that defines the allergic response as self-limiting [(5)].

Lipoxygenase products:

Nonsteroidal anti-inflammatory agents such as aspirin and indomethacin block the cyclooxygenase pathway, but they do not inhibit the production of the lipoxygenase products of arachidonic acid. Steroids prevent the release of arachidonic acid from membrane phospholipids, perhaps by the formation of peptide inhibitors of phospholipase A2, thus blocking both the cyclooxygenase and lipoxygenase pathways. Therefore, steroids have the ability to block the production not only of prostaglandins and thromboxanes, but also of leukotrienes[(5)].

1.2.2.6 Immunoglobulins:

Immunoglobulins, or antibodies, are the glycoprotein products of antigen-stimulated B cells. The only function of specialized, terminally differentiated B cells, called plasma cells, is the production and secretion of large amounts of immunoglobulin, which is found in both membrane-bound (serving as B-cell surface receptors) and soluble forms. They are widely distributed in plasma and secretory fluids such as tears, milk, and mucous.

Immunoglobulins may be divided into different classes based on certain physiochemical characteristics. The common physiochemical and antigenic properties of each class are based on shared regions of heavy-chain amino acid sequences. There are five basic classes, or isotypes: IgM, IgD, IgG, IgA, and IgE [(5)].

IgM plays a significant role in the primary immune response. It is found as a pentamer and accounts for approximately 10% of immunoglobulins.

IgG is the most abundant immunoglobulin in normal human serum, accounting for approximately 75% of the total immunoglobulin pool.

IgA plays a major role in mucosal immunity. Dimeric IgA binds to specific Fc receptors, "secretory components," on epithelial cells of organs such as the intestine, as well as on the conjunctival surface. The secretory component shuttles the dimeric IgA through the cell until it is cleaved at the luminal side. Hence, dimeric IgA enters the mucosal lumen where it can neutralize pathogens. IgA is the predominant immunoglobulin in tear fluid, milk, saliva, and tracheobronchial secretions.

IgE usually is found in small amounts in the serum of normal individuals but may be increased greatly in patients with atopic disease. It is responsible for immediate hypersensitivity reactions and for immunity to parasites. CD4+ TH2 cells produce IL-4, which promotes the production of IgE. IgE with specific epitopes to allergens has been isolated in the tear fluid of patients with atopic disorders.

IgD found on the surface of 50%of B lymphocytes is the least common immunoglobulin [(5)].

1.2.3 Immunopathology

The components of the immune system work together to ensure the destruction and the elimination of foreign organisms or potentially harmful substances globally seen by immunocompetent cells as antigens. In certain situations, the immune inflammatory response may be exaggerated and inappropriate, leading to damage to the organism's own tissue in the attempt to eliminate the offending agent. These abnormal hypersensitivity reactions can be divided into four major groups. The first three are primarily mediated by antibodies, whereas the fourth is primarily cell dependent [(5)].

Type I Hypersensitivity:

Type I hypersensitivity, also known as mast cell–mediated hypersensitivity, is a term that describes a series of events that culminate in the activation of a unique set of effector cells known as mast cells, resulting in mediator release and consequent tissue inflammation[(5)]. The initiating event is the interaction between an antigen and its specific IgE previously bound to the surface of tissue mast cells, resulting in mediator release and consequent tissue inflammation[(6)]. This interaction is specific and requires prior

sensitization. The initial response seems to be the first part of a more complex reaction that involves production of mediators denovo and their release at a later time to further extend the inflammatory reaction by recruiting other effector cells, primarily eosinophils. This constitutes the late-phase reaction and plays a central role in perpetuating the deleterious effects of immediate hypersensitivity. IgE-mediated mast cell activation is the basic mechanism of allergic reactions and atopy. The initial contact with an antigen leads to specific immunoglobulin E (IgE) synthesis by B cells. Secreted IgE binds to mast cells or basophils through high-affinity Fce receptors (FceRI). On subsequent exposure to antigen, an immediate hypersensitivity reaction is triggered by cross-linking the IgE molecules. Environmental factors certainly contribute to the generation of clinically significant allergic reactions, but their role has yet to be defined.

A prerequisite to immediate hypersensitivity is the production of specific IgE by B lymphocytes after initial exposure to an antigen. These immunoglobulins are subsequently bound to Fc receptors on the surface of mast cells and basophils. When the organism is re-exposed to

the same antigen, this interacts with the surface-bound IgE, causing cell activation. For antigen antibody interaction to activate the cell effectively, cross-linking of at least two adjacent IgE molecules must occur.

Preformed mediators are released from cytoplasmic granules by exocytosis. The type and number of mediators produced and released by mast cells seem to vary with their anatomic location. So-called mucosal mast cells, found in the gastrointestinal tract, contain chondroitin sulfate as their major granule proteoglycan and little histamine, whereas connective tissue mast cells, which are the predominant cell type of the periocular tissue, contain heparin and release large quantities of histamine. This vasoactive amine acts systemically and plays a dominant role in determining the clinical manifestations of immediate type hypersensitivity. It remains the primary target of most therapeutic interventions. Several enzymes present in the granules, which also are released in this phase of the reaction, may cause local tissue damage, and contribute to injury. Activation of mast cells in the ocular mucosa leads to chemosis, angioedema, and conjunctivitis [(5)].

Type II (Cytotoxic) Hypersensitivity:

In type II hypersensitivity IgG, IgM, and rarely IgA mediate antiself reactions that are directed against antigens on the surface of one's own cells. The target cells may be circulating or components of fixed tissue and antibody-antigen interaction leads to cell lyses [(5)]. Type II hypersensitivity responses are observed in transfusion reactions, hemolytic anemia, Good pasture's syndrome, pemphigus and myasthenia gravis [(6)].

Type III Immune Complex Hypersensitivity:

Reactions which involve type III hypersensitivity responses also are termed immune complex diseases. Under normal conditions, when an antibody and an antigen combine, an immune complex is formed. These complexes usually are cleared from the systemic circulation by phagocytes. Ineffectively cleared immune complexes that persist in the circulation can lead to systemic disease. This type of hypersensitivity is responsible for diseases such as systemic lupus erythematosus, polyarteritis nodosa, serum sickness and phacoanaphylaxis [(6)].

Type IV Delayed Hypersensitivity:

Delayed-type hypersensitivity is a cell-mediated immune reaction, and unlike the other three types of hypersensitivity is not antibody dependent. Recognition of foreign substances resides in specific receptor molecules present on the membrane of T cells and not in humoral antibodies secreted by B cells[5]. A common trend in these diseases is that the causative agent persists, generating a chronic antigenic stimulus. The pathogenesis of sympathetic ophthalmia is mediated via a type IV reaction [6].

1.2.4 Vernal Keratoconjunctivitis

1.2.4.1 Definition:

Vernal keratoconjunctivitis (VKC) is an allergic conjunctival inflammatory disorder with (in most cases) an associated secondary keratopathy. VKC is characterized by the classic hallmark of giant papillae, usually in the upper tarsal conjunctiva but in some instances in the conjunctiva at the corneoscleral limbus [16.17].

It is also defined as a bilateral, recurrent inflammation of the conjunctiva [4.18.19].

1.2.4.2 Epidemiology:

VKC has a worldwide distribution, with pronounced regional variations and prevalence [16]. The highest incidence of the disease is in the warm temperate [4], Middle East-Mediterranean region, and Mexico [6]. It is relatively rare in North America and Northern Europe. It may represent as much as 3 percent of serious ophthalmic disease in some regions whereas in Northern Europe and North America the prevalence is approximately 1 in 5000 cases of eye diseases[16].

Age:

Most series agreed that it affects children and young adults. Albert and Jakob found that VKC has been reported to affect patients from 1 month of age to more than 70 years of age, but at least 50 percent of the patients in most reported series are between 5 and 25 years of age [16]. The peak age of onset is 8 to 12 years, although 10% of VKC patients are older than 20 at age of onset [5]. Others describe it as most common in children between the ages 3 and 16 [20] or the age range 5-20 years, with peak incidence in the age range 11-13 years [6].

Sex:

Vernal conjunctivitis most often affects young boys [18, 19, 21]. Boys are affected twice as frequently as girls [6, 22]. A study by Sayegh F and his collogues found that male children were affected about three times more frequently than females [23]. But the male-to-female ratio evens out when the disease affects adults [6, 22].

While most series describe a male preponderance one series points out a female preponderance of patients with limbal vernal conjunctivitis when cases are stratified by sex[5].

Seasonal variation:

Vernal is the Latin word for spring. It is a poor name because it is more common in climates where there is no spring [20]. It occurs with the onset of hot weather [18,19], and therefore rather a summer than a spring complaint [18]. The symptoms and signs of VKC may occur on a seasonal basis with a peak incidence between April and August but many patients have a year-round disease [4,20,23].

The increase in the pollen count, possibly account for exacerbation in the spring [5,6, 21].

Family history:

A family history of atopy is very common [6]. There is evidence that VKC is an allergic disease, appearing in patients who are atopic (i.e., having signs of asthma, eczema, or hay fever) [5]. About three quarters of patients have associated atopy and two third have a close family history of atopy [4].

The majority of cases of VKC develop a spontaneous remission of their disease after puberty [24]. They have a spontaneous resolution of the disease within 10 years of its onset [16]. Children usually have self-limited dieses and eventually grow out of the disease over a period of 5-10

years. Some young adults develop more severe manifestation of the disease some times with indefinite recurrences [6, 18].

1.2.4.3 Clinical Feature:

Symptoms: the main symptoms are intense ocular itching associated with lacrimation, photophobia, F.B sensation and redness this accompanied by a characteristic white ropy secretion caused by increase of viscous mucous in tears[4,18,20,24].

Signs: Three forms of the disease occur; palpebral, limbal and mixed.

The palpebral form is marked by cobblestone papillae on the superior tarsal conjunctiva, while the lower lid is affected minimally.

The limbal form is marked by a broad, thickened, gelatinous opacification of the superior limbus that can over-ride the cornea [6].

Limbal signs are more common in dark skinned races while tarsal and corneal signs predominate in lighter skinned races.

Mixed form in which palpebral and limbal signs coexist [4].

1.2.4.4 Pathology:

Conjunctiva:

Tarsal conjunctiva may undergo hyperplasia of its epithelium and proliferation of fibrovascular connective tissue along with an infiltration of round inflammatory cells especially eosinophils and basophils [19]. It is easily recognized on everting the upper eyelid, palpebral conjunctiva is seen to be hypertrophied and mapped out into polygonal raised area [18]. As the disease progresses the papillae become larger and joined together to produce giant papillae [20]. Papillae that have enlarged often having flatten tops. Papillae can be distinguished from follicles by their red centers; these centers consist of dilated blood vessels at the core of the papillae surrounded by inflammatory cells [5]. Papillae that form as the result can become quite large clinically resembling cobble stone [19].

A sequel that may occur in VKC is conjunctival scarring that has a lacy appearance at the base of the old papillae. Although rare, there may be lacy scarring that extends superiorly into the fornix. On rare occasions there may be conjunctival cysts and enough scarring to cause symblepharon formation [5].

Limbus:

The epithelium and subepithelial fibrovascular connective tissue of the limbal conjunctiva region may undergo hyperplasia and round inflammatory cells infiltration with production of limbal nodules [19]. These changes are recognized as thickening and opacification of the limbus [5]. Limbal nodules appear as gelatinous elevated lesions of the superior limbus that can over-ride the cornea [5,6,18]. These lesions may seem to coalesce and become confluent [5]. A very characteristic manifestation of limbal vernal conjunctivitis is the presence of Horner-Trantas' dots, which are white, chalk-like dots composed of eosinophils and epithelial debris [6,18].

Cornea:

The cornea can be involved in up to 50% of cases [6]. It may be severe enough to interrupt a child's education, or if uncontrolled it may cause permanent corneal scarring and loss of vision [5]. Degenerations and death of corneal epithelium result in punctate epithelial erosions that are especially prone to occur in the upper part of the cornea [19]. If the inflammation continues, with an outpouring of inflammatory mediators into the tear film with associated

epithelial toxicity and possibly conspiracy from the mechanical effects of the large papillae, a frank epithelial defect appears next. Such defects have been termed shield ulcers because of their position and morphology [16]. A vernal ulcer of the cornea is a horizontally oval, shallow, nonvascularized, indolent ulcer of the superior cornea. The edges are composed of shaggy, gray, dead epithelial cells, and there is infiltration of the underlying superficial stroma. After the ulcer heals, a mild corneal opacity may persist at the level of Bowman's layer [6]. In general, these ulcers are sterile, but there have been rare reports of superimposed infectious corneal ulcers occurring in VKC [5].

Mucus:

VKC is often accompanied by a thick, tenacious mucous discharge that may be so thick that it adheres to the giant cobblestones of the upper tarsus. When removed, it may form a cast of the cobblestones. Patients report symptomatic relief when the stringy, ropy secretions are removed from the cul-de-sac [5].

1.2.4.5 Pathophysiology:

Type I Hypersensitivity:

The physiopathology is considered to be of type I hypersensitivity reaction (IgE mediated) [25].The mechanism of the disease involves fixation of IgE molecules on the surface of mast cells and release of mediators, including histamine and prostaglandins. Frankland and Easty noted that 93% of their 35 patients from the United Kingdom had manifestations of atopic disease, including asthma, eczema or hay fever, but 7% did not [5]. In a survey of IgE levels in VKC patients in Israel, tear IgE levels were significantly increased in 63.5%, but in 29% of the patients both tear and blood IgE levels were normal to low [26]. In another study, serum IgE levels were elevated in 75% of patients [5].

Following allergen challenge, tear levels of histamine, kinins and thromboxane TxB2 are all elevated [22]. In GPC, 30% of mast cells appear to be in a degranulated state, while in VKC this increases to 80%[10].

Delayed Hypersensitivity:

It has been suggested that there is a cell-mediated component in vernal conjunctivitis as well, and this has been substantiated by studies of the conjunctiva of patients

with vernal conjunctivitis [27]. In chronic allergic disorders (AKC, VKC and GPC), CD4+ T-cells numbers are increased, with a mixed cellular infiltrate containing many mast cells, eosinophils, neutrophils, and macrophages. [26] This increased number of T4 helper/inducer cells has been confirmed and a further study has shown these cells to be the type that can induce the production of IgE antibody [28]. Abu El-Asrar found numerous stromal lymphocytes. A specific type of delayed hypersensitivity known as cutaneous basophil hypersensitivity has also been implicated and in an animal model the influx of eosinophils as well as basophils has added evidence that this type of hypersensitivity may be operant [5].

1.2.4.6 Treatment:

Nonspecific:

Cold compresses may alleviate the itching in vernal conjunctivitis when it is mild [6, 18]. However, when the disease is more severe, this treatment is usually not effective by itself [5].

Allergen Avoidance:

The mainstay of therapy is allergen avoidance [29,] which is best evaluated by an allergy specialist [17].Although it is usually an unpleasant, expensive, time-consuming, policing the patient's environment and scrupulously cleaning it of all potential allergen provocateurs is critical to the long-term stability of patients with VKC. Involvement by a truly expert allergist, who not only can perform the appropriate patch, scratch, and prick tests, as well as serum radioallergo - sorbent test (RAST), but who also can perform the environmental detective work and the motivational and educational work necessary for a successful environmental control program, is essential. Obviously, the family must be convinced of the long-term benefits, not only to the patient but also to the family as a whole, before they will seriously embark on a complex program that sometimes involves removal of expensive carpeting, installation of air conditioning, installation of air-filtering systems in the home heating system, elimination of beloved pets, and other measures. The wisdom, importance, and usefulness of this component of the patient's care cannot be over emphasized [16].

Systemic Medication:

Systemic antihistamines is, superior to topical ocular antihistamine therapy in patients with the complicated allergic eye diseases, primarily because these diseases last so long but also because these allergic individuals sometimes become sensitized to the preservatives present in the commercially available ocular antihistamines [16]. The use of terfenadine, 60 mg twice a day, or astemizole, 10 mg twice a day, or both, is usually sufficient [16,17]. They are second generation H1-receptor antagonist. Unlike the first generation they do not cross the blood brain barrier to any appreciable extend and thus minimally sedating [29].

Systemic desensitization immunotherapy may be indicated in the patient who has striking sensitivity to a limited number of allergens. Performing desensitization immunotherapy on a patient with ocular allergy, however, is not easy, and some features of this practice are different from the typical practice of desensitization immunotherapy in the patient with allergies not affecting the eyes [16].

Topical Medication:

Topical treatment offers several obvious advantages. Eye drops are easily applied and seldom lead to systemic

side effects. Also, the physical presence of the drops themselves will have a washout effect, helping to remove the inflammatory mediators and thereby lessening some of the symptoms. Topical treatment may also have some disadvantages. Vasoconstrictor drops only act for a short time and can lead to a rebound vasodilatation [22]. Topical steroids are effective in reducing the influx of inflammatory cells but have little effect on mast cell mediator secretion, are slow to act and take several days to achieve their maximal effect. They may also have serious side effects, such as producing glaucoma, causing cataracts, and potentiating infection [24], and so should not be used routinely in these conditions.

Mast cell stabilisers, such as sodium cromoglycate, carry very few side effects, but patients need to receive treatment for several days before the expected exposure to allergen, reducing the tryptase and inflammatory cells after allergen challenge [22].Maintenance with these topical mast cell stabilizing agent during the seasonal period of activity generally keep the symptoms in check [18].

Antihistamine-Vasoconstrictors:

Until recently, topical formulations of antihistamines which were developed primarily for systemic administration, although having some beneficial effects, were usually not potent enough for monotherapy, and had to be administered with vasoconstrictors [22]. These preparations may have some role in the treatment of mild vernal conjunctivitis; however, in the face of onset of any keratitis, they do not have the potency necessary to control the inflammation [5].

Levocabastine, developed for topical administration, acts within 10 minutes, has a high speed binding affinity for histamine H1 receptors, but does not interact with cholinergic receptors and has few systemic side effects [22].In double-blind comparison of levocabastine eye drops with sodium cromoglycate, particularly at high-pollen days, levocabastine was superior to cromoglycate in eliminating moderate or severe symptoms [30,31].

Mast Cell Stabilizers:

A series of sequential events occurs in the conjunctival mast cells of patients with VKC resulting in the release of inflammatory mediators. Several agents, such as disodium

cromoglycate, have been designed to interfere with the release of the mast cell mediators [6, 24], and for the treatment of VKC [5]. Mast cell stabilizers are one of the most commonly used antiallergic agents in ophthalmology world wide [29].

Examination of the first report of cromolyn in VKC is important to understand possible differences between various studies. In this pioneering study, most patients with VKC could be controlled with cromolyn alone. However, some required short-term corticosteroids in addition to cromolyn, and others required long-term corticosteroids in addition to cromolyn. This emphasizes the prophylactic nature of the drug and its steroid-sparing qualities [5].

Mast cell stabilisers act by preventing calcium influx into the mast cells and basophills thus preventing the cascade that result in degranulation [29, 32]. These are proton H_1 receptor antagonists. Once these mast cells inhibitors are bound to a membrane receptor they prevent IgE cross linking and thus stabilises the entire excitation process. Their mechanism of action also involve increasing intracellular cyclic adenosine monophosphate levels thereby reducing calcium influx or by inhibiting the enzyme

nucleosides diphosphate kinase in the cytoplasm. Mast cell stabilizers can also act by inhibiting the release of neuropeptides from sensory nerve ending [29,33].

The various agents of this group used in ophthalmology are as follows:-

Cromolyn Sodium (Sodium cromoglycate):

Indications: in the treatment of allergic ocular disorders including vernal Keratoconjunctivitis, giant papillary conjunctivitis vernal keratitis and allergic conjunctivitis [29, 34, 35].

Sodium cromoglycate inhibits the degranulation of sensitized mast cells [20,29]and basophils which occur after exposure to specific antigens thus inhibiting the release of histamine and SRS-A (slow reacting substance of anaphylaxis) from the mast cells[6,29]. It has no intrinsic vasoconstrictor, antihistamine or anti-inflammatory activity [29]. Sodium cromoglycate is poorly absorbed and approximately 0.03% of it is absorbed following topical administration to the eye [29, 32]. Systemically absorbed drug is excreted unchanged in the urine. Less than 1%of administered dose penetrates into the aqueous humor, and

clearance from this chamber is almost complete within 24 hours following discontinuation of treatment [32].

Onset of therapeutic effect: usually within few days [22, 32]. One study suggest that it acts within minutes. Sodium cromoglycate was statistically better than placebo in reducing the symptoms at 2, 10 and 30 minutes after the treatment had been administered, showing that topical application of 2% sodium cromoglycate can quickly relieve ongoing symptoms of allergic inflammation in the eye[36].

Contraindications: Hypersensitivity to any component of its product [29]. One patient with an immediate type I reaction to DSCG is reported [37].

Patients are advised not to wear soft contact lenses during treatment [29]. Although Iwasaki W conclude that commercial DSCG applied topically to contact lenses does not result in the accumulation of either the drug or its preservatives in lenses and that DSCG can be safely applied directly onto a worn contact lens[38].

Dosage: 1-2 drops in each eye, 4-6 times a day at regular intervals till the desired effect is obtained [29]. In a study to compare the efficacy and side effects of sodium cromoglycate, eye drops (Opticrom 2%) used (regularly)

versus (as needed) in the treatment of seasonal allergic conjunctivitis. It showed that there is additional therapeutic benefit from using sodium cromoglycate eye drops regularly throughout the ragweed pollen season [39].

It is effective alone or in combination with other anti-allergic drugs (topical or systemic). Symptomatic response to the therapy is usually evident within few days but treatment should be given up to six weeks or more. The effect of therapy depends upon administration at regular intervals and continuity as long as needed to sustain clinical improvement. Topical corticosteroids can be used concomitantly with cromolyn sodium [29].

Adverse reactions: The most frequent adverse reaction reported is ocular stinging or burning sensation upon instillation which usually regresses with continued use. Other adverse effects reported are conjunctival injection, watery itchy and puffy eyes, dryness, irritation and styes [29]. However, cromolyn is usually not adequate when the eye is severely inflamed or when there is a vernal ulcer [5]. A good strategy by which to control the acute exacerbation of symptoms is to start with frequent topical corticosteroids combined with topical cromolyn. The corticosteroids are

then tapered off over a 2-3 week period as the therapeutic effects of the cromolyn take hold [6].

In a double blind study of 22 patients with vernal catarrh, sodium cromoglycate eye drops improve the condition of the treated eyes. A long term study of up to two years in 61 patients showed that Keratoconjunctivitis could be controlled without topical steroid in 11 patients and with only short periods of steroid therapy in 44 patients [33]. Another study showed that patients using sodium cromoglycate were 17 times (95% confidence interval) more likely to perceive benefit compared with those using a placebo [40].

In 144 subjects, all had at least a 2-year history of seasonal allergic conjunctivitis and were symptomatic at the time of inclusion, results for the decrease of main allergic conjunctivitis symptoms (itching, tearing and redness) showed a marked effect for active treatment on day 3 with a sustained improvement on days 7 and 14. A clear response to treatment (an improvement of sum scores for day 3 of >/=3 points compared to baseline) occurred in 83.0% of sodium cromoglycate patients and 56.3% of placebo

patients [41]. The same result was obtained in another study [42].

Topical 4% disodium cromoglycate was found to decrease the levels of tryptase in tears of patients with VKC from 16.77 ng/mL to 7.29 ng/mL[12].

When comparing 4% disodium cromoglycate and 2% disodium cromoglycate; the results indicate that the use of 4% sodium cromoglycate eye-drops twice daily is as effective and well tolerated as 2% sodium cromoglycate four times daily in the treatment of birch-pollen conjunctivitis[43].

In a retrospective clinical case study**;** concurrent use of a steroid and DSCG provided the most efficacious treatment modality for VKC [44].

Sodium cromoglycate effects on VKC in children:

A double-masked, coded trial was undertaken to evaluate the effect of the topical administration of 2% cromolyn sodium eye drops on vernal keratoconjunctivitis in 14 children. One eye of each patient was treated for one year with cromolyn, the other eye with placebo. Cromolyn reduced the characteristic vernal keratitis, vernal corneal ulcers and plaques, and limbal oedema and infiltrates but

did not affect the number or size of the giant papillae. The drug's long-term topical use did not have any adverse side effects [45].

In black children in Southern Africa a combination of steroids and SCG proved particularly effective in treating severe cases, indicating a possible synergistic effect of the 2 drugs [46].

Nedocromil:

It is a disodium salt of pyranoquinoline dicarboxylic acid. Nedocromil prevents chemotactic and inflammatory mediator release from the effector cells such as granulocytes, monocytes, macrophages and mast cells [29]. In comparison to DSCG, nedocromil is more effective in controlling symptoms of VKC [47], but when compared with fluorometholone, fluorometholone was significantly more effective than Nedocromil [24].

It is tried in concentration of 1 percent to be given 1-2 drops 4 times a day. No serious side effects have been reported with the use of this drug.

Lodoxamide:

It is a most potent topical mast cell inhibitor. It effectively

prevents histamine release from mast cells during immediate hypersensitivity reactions.

Lodoxamide significantly reduces recruitment of neutrophils and eosinophils and prevents mast cell degranulation. Inhibition of leukocyte, monocyte and eosinophils activation by mast cell stabilizers is important in modifying the allergic inflammatory response. It stabilises the mast cell response in vernal conjunctivitis and has dual mechanism of action.

Indications: it is highly effective in treatment of vernal Keratoconjunctivitis (VKC), giant papillary conjunctivitis (GPC) and atopic Keratoconjunctivitis (AKC). Lodoxamide is more efficacious than DSCG with earlier improvement of signs and symptoms [48].It is most effective in VKC and for sustained relief of signs and symptoms and treatment of corneal complications.

Dosage: it is available as 0.1 percent ophthalmic suspension (Lodoxamide tromethamine). The usual dosage is to instill 1-2 drops in the affected eyes 4 times a day throughout the year. It should be instilled at regular intervals for better response.

Adverse reactions: adverse effects have been reported with topical lodoxamide use; transient burning and stinging

sensation, ocular itching, dry eye, blurred vision, tearing, discharge, hyperemia, crystalline deposits, foreign body sensation, rarely chemosis, corneal abrasion, keratitis, blepharitis, allergy, etc, which regresses with regular and continuous use of lodoxamide [29].

Other new mast cell inhibitors:

Ketotifen fumarate:

Ketotifen is a relatively selective non competitive histamine antagonist (H_1 receptor and mast cell stabilizer). Ketotifen inhibits the release of mediators from cells involved in hypersensitivity reactions. Decrease chemotaxis and eosinophils activation have also been shown.

Indications: it is indicated for the treatment of allergic conjunctivitis of diverse etiology [29].

A single dose of ketotifen was superior to a 2-week four-times-daily regimen of cromolyn in alleviating symptoms of allergic conjunctivitis [49].

Dosage: It is available as 0.025 % topical solution in 5 ml and 7ml packs. Recommended dose is to instill one drop in each affected eye every 8-12 hours. This solution is for topical ophthalmic use only. It is not recommended for

injection or oral use. It is contraindicated in patients who are hypersensitive to any component of the product.

Adverse reactions: generally topical ketotifen solution is safe for ophthalmic use. However in less than 5 % of patients the following ocular adverse affects may appear; burning or stinging sensation, allergic reaction, conjunctivitis, discharge, dry eyes, keratitis, lacrimation disorders, photophobia and rash may occur. General adverse effects may include flue syndrome and pharyngitis. In pregnant, lactating mothers and children below three years of age its use is not generally recommended.

Olopatadine hydrochloride:

Olopatadine is a new agent that exerts both mast cell stabilization effect and antihistaminic effect. It is highly potent and relatively selective H_1 receptor antagonist that inhabits in vivo and in vitro type-1 immediate hypersensitivity reaction. It has no effect in alpha adrenergic dopamine muscarinic type 1 and 2 and serotonin receptors.

Olopatadine has been reported to have low systemic exposure following topical administration. Clinical trials had shown that it has more than 90 percent inhibition of

basophill and mast cell degranulation and histamine induced conjunctival vascular permeability.

Olopatadine is indicated for the treatment of allergic conjunctivitis of diverse etiology.

Dosage and administration: Olopatadine is available as 0.1% topical ophthalmic solution in 5ml vial. The recommended dose is 1-2 drops in each affected eye 3-4 times per day (every 6-8 hours).

Olopatadine ophthalmic solution is available for topical use only. It is contraindicated in those patients who are hypersensitive to any component of this product.

Patients are instructed not to wear contact lenses during treatment with olopatadine. In pregnant, lactating mothers and children below 3 years of age, its use is not generally recommended.

Adverse reactions: Ophthalmic adverse effects reported are burning or stinging sensation, dry eye, foreign body sensation, hyperemia, lid oedema and pruritus.

Systemic effects include headache, cold syndrome, pharyngitis, sinusitis and taste perversion [29].

Prostaglandin Inhibitors:

Coincident with his studies on the effect of prostaglandins on the outer eye, Abelson and his co-workers suggested the use of oral aspirin in the treatment of VKC [8]. The efficacy of aspirin was also confirmed in other studies [50].

Aspirin: has been proved effective in controlling symptoms in patients of VKC unresponsive to sodium cromoglycate and corticosteroid.

Dosage: 0.5-1.5gm daily for 4-6 week period [29].

Topical NSAIDs: Are effective in ocular allergy.

Topical suprofen (1%) is effective in managing the signs and symptoms of VKC.

Dose: 1-2 drops 3 times a day for 4-6 weeks [29].

Ketorolac (Acular) is a nonsteroidal anti-inflammatory drug that blocks the release of prostaglandins by blocking enzyme cyclooxygenase and breaks the itch-rub cycle.

Dosage: 1 drop 4 times a day [5].

Corticosteroids:

Corticosteroids inhibit mediator biosynthesis and disrupt intercellular communications by preventing the release of lymphokines. They are the most effective and the best-

proved treatment for VKC especially when the keratitis is active. If possible, a weak steroid such as flouromethalone should be used rather than dexamethasone or prednislone. This is because even when used for prolong periods, flouromethalone does not usually results in elevation of IOP in susceptible individuals [4] and proved to be safe in children [5,6,16,18,29].

Acetylcysteine:

One of the common clinical findings is the tenacious mucus that develops. This may take any of three forms: mucus adhering to the cobblestones, thick and ropy strands of mucus or filamentary keratitis. Acetylcysteine is known to break the disulfide bonds, thereby dissolving the mucus and it is effective for all three types of excessive mucus [4, 5].

Immunosuppressive Agents:

Immunosuppressive medication may be beneficial. Cyclosporin A binds to cyclophilin, an intracellular protein, which in turn prevents the formation of interleukin-2 and the subsequent recruitment of activated T cells. It has been used successfully to treat VKC.

Topical cyclosporine 2%has been clinically tried with a dosage of one drop 4 times a day. There was complete

improvement in symptoms in more than 80% of cases with VKC. Unlike systemic cyclosporine, topical preparations are relatively free of adverse effects and hold a promising future in the treatment of various ocular allergic disorders [4, 5,29].

Cryotherapy:

Several reports have advocated the use of cryotherapy in the treatment of VKC. Sankar kumar and colleagues treated the conjunctiva of 30 eyes in 15 patients with a glaucoma probe at -60°C and -80°C, repeating the freeze-thaw cycle two to three times. They concluded that cryotherapy was helpful in the management of limbal nodules of VKC. However, they also gave the patients 0.5 to 1.5 g of aspirin. Therefore, it is difficult to distinguish the effect of the cryotherapy from that of the aspirin [5].

Surgery:

Surgical removal of a plaque in the base of a vernal ulcer preventing re-epithelialization may promote healing. Tarsectomy with or without mucous membrane graft has been suggested to physically remove the cobblestone papillae. However, these reports appear to lack long-term follow-up. Mucous membrane grafting has been reported to improve symptoms in vernal conjunctivitis, although there

has been controversy in the literature regarding this procedure [5, 51].

ß-Irradiation:

Several authors have reported success with ß-irradiation in the treatment of VKC. However, one of the authors of this article (ELS) has seen permanent scarring from this treatment, and the lack of publications in the modern literature suggests that this mode of therapy no longer has a place in the treatment of VKC. [5]

1.3 OBJECTIVES

1.3.1 General objective:

This study aims to evaluate from a clinical point of view the role of sodium cromoglycate in treatment of VKC.

1.3.2 Specific objectives:

- To specify the effect of sodium cromoglycate in reliving symptoms and signs of VKC.
- To detect the efficacy of sodium cromoglycate as a prophylactic therapy decreasing the frequency of attacks of active VKC.

CHAPTER TWO

2.1 MATERIAL AND METHODS

2.1.1 Setting:

In this study 97 patients of both sex with VKC were clinically studied during the period from Jan. to June 2004.

2.1.2 Study design:

This is a single masked interventional case control hospital based study.

The study sample was randomly divided into two groups:

A study group of 68 patients received sodium cromoglycate and a control group of 29 patients received tears naturale as placebo for comparison.

2.1.3 Study Area:

This study was conducted in Makkah Eye Complex Khartoum- Sudan.

2.1.4 Study Population:

Ninety-seven patients (59 males and 38 females) with VKC were included in this study. Their mean age was 11.32 years, ranging from 2 to 34 years.

2.1.5 Inclusion and Exclusion Criteria:

2.1.5. 1 Inclusion Criteria:

-All patients with VKC who had not received any VKC targeted therapy for a period of 2 weeks before the study.

-Patients discovered and diagnosed for the first time as VKC cases (not treated before).

2.1.5.2 Exclusion Criteria:

-All patients with VKC who were taking medications two weeks prior to the first day of examination (base line examination).

-VKC patients who received sodium cromoglycate before as treatment alone or as a part of medical therapy.

-Patients who developed hypersensitivity for sodium cromoglycate or its preservative.

-Patients with vernal ulcer.

2.1.6 Procedure:

The diagnosis of VKC was based on history of symptoms (redness, itching, tearing, etc) and signs (conjunctival papillary hypertrophy, giant papillae, hyperaemia, gelatinous infiltration of the limbus, Trantas' dots and superficial punctate keratitis).

2.1.6.1 The Questionnaire:

A questionnaire was pre-coded and contains information concerning:-

-Personal data.

-History of systemic and ocular diseases.

-Family history of VKC or other atopy.

-Medication used before.

2.1.6.2 Examination:

A full ocular examination was performed by the author and the symptoms and signs were graded and recorded.

1st day examination = base line examination

1st visit = after two weeks

2nd visit = after four weeks

2.1.6.3 Treatment:

Steroid: (in a form of flouromethalone 4times per day) was given to all patients in the 1st day and stopped in the 1st visit.

Sodium cromoglycate: (4 times per day 2% for children below 16 years of age and 4% above that) was given to the study group in the 1st day and continued till the 2nd visit.

Tears naturale: (4times per day) was given to the control group as placebo in the 1st day and continued till the 2nd visit.

2.1.6.4 Grading of Symptoms and Signs:

-Grading of symptoms and signs was done at the visit time.

-In young children grading of symptoms was depend on their parent's opinion.

2.1.6.4.1 Grading of Symptoms:

The major symptoms of VKC including itching, watering, redness, photophobia, foreign body sensation, and discharge were recorded separately and graded. We applied grade 0 for no symptoms, grade 1 for mild symptoms, grade 2 for moderate symptoms, and grade 3 for severe symptoms.

2.1.6.4.2 Grading Of Signs

The following signs were assessed: hyperaemia, gelatinous infiltration of the limbus, punctate keratitis and Trantas' dots. Hyperaemia and gelatinous infiltration of the limbus were graded as follows: 0 = none, 1 = mild, 2 = moderate, 3 = severe. Punctate keratitis was graded as follows: 0 = none, 1 = 1 quadrant affected, 2 = 2 quadrants affected, 3 = 3 or more quadrants affected. Trantas' dots were graded as follows: 0 = none, 1 = 1 dot, 2 = 2 or 3 dots, 3 = more than 3 dots.

2.1.7 Study tools:

Materials in this study include:-

- Snellen chart
- Light pin tourch
- Direct ophthalmoscope
- Slit lamp
- Eye drops (local anaesthesia and mydriatic)

-Fluorescein strips

-Trial set

-Retinoscope

2.1.8 Data Analysis

The data was analyzed by SPSS-12 software.

2.1.9 Ethical consideration

A verbal consent was taken from the patients or the parents in cases of small children included in this study.

2.1.10 Limitation of the study

-Patients enrolled but not complying with the treatment schedule or follow up were excluded.

CHAPTER THREE

3 RESULTS

3.1 Socio-demographic data:

3.1.1 Age distribution among the study population:

Most of the study population was below the age of 20 years (92%) with the peak age between 10-14 years (table3.1).

3.1.2 Sex distribution among the study population:

Fifty nine patients (61%) were males and 38 patients (39%) were female (figure 3.1) and (table3.1).

3.1.3 Distribution of the study population according to residence:

Most of the patients were living in Khartoum state but originally they were from Northern Sudan (45%), Western Sudan (38%), Central Sudan (13%), Southern Sudan (2%) and Eastern Sudan (2%) (figure 3.2).

3.2 Past ocular history:

Seventy eight patients (80.4%) had a past history of VKC and 19 patients had no past history of the disease (figure 3.3). Six patients only had a past ocular history of keratoconus (three patients), squint (two patients) and retinitis pigmentosa (one patient).

3.3 Family history of VKC or other atopy among the study population:

Sixty two patients (64%) had no family history of VKC and 22 patients had a family history of other atopy e.g. asthma, eczema (table3.2).

3.4Presenting complaints (symptoms) of the study population:

3.4.1Base line presenting symptoms:

Almost all patients (except one) were complaining of itching at presentation, 82%of them had its severe form, 64% of the patients complained of severe redness or discoloration of their eyes. About one third of the patients (33%) presented with severe photophobia, 42.3% presented with severe lacrimation, 34% presented with severe mucoid discharge and 41.5% of the patients presented with severe foreign body sensation (table3.3).

3.4.2 1st visit (after two weeks)

By the end of the first two weeks there was a remarkable improvement in both study and control groups. This improvement was statistically significant since the P value was 0.00.

This improvement manifested among the study group (using sodium cromoglycate and steroid) as follows; lacrimation and discharge disappeared completely or became minimal in 95% of

patients, (tables 3.6, 3.7), photophobia disappeared or reduced significantly in intensity in 89.7% of patients (table3.5), 89% of patients had no more or just mild itching (table3.4), 82.3% of patients declared that they have no more or just mild eye redness (table3.9), foreign body sensation became absent or minimal in 58.7% of the patients (table3.8).

Among the control group (using placebo and steroid) the presenting symptoms improved as follows: photophobia disappeared or reduced significantly in intensity in 93% of patients (table3.5), discharge and lacrimation disappeared completely or became minimal in 89.7% and 82.7% of patients successively (table3.7) and (table3.6), 79.3% patients had no more or just mild itching and redness (table3.4, 3.9), foreign body sensation became absent or minimal in 75.8% of the patients (table3.9).

3.4.3 2nd visit (after four weeks)

In the second follow up visit the improvement that achieved in the first visit was maintained in the study group (using sodium cromoglycate only). Itching, lacrimation and discharge remained in the mild form or disappear completely in a significant percent of patients (tables 3.4, 3.6, 3.7).

Further significant improvement occurred regarding photophobia foreign body sensation and redness (tables 3.5, 3.8, 3.9). P value < 0.05.

The picture was totally different in the control group. Regarding photophobia, discharge and foreign body sensation there was no significant change from first follow up visit (tables 3.5, 3.7, 3.8). There was significant diminution in the number of patients who had mild or no itching (62%) (table3.4). Lacrimation became absent or mild in only 79% of patients (table3.6). Redness disappeared or became mild in only 69% of patients (table3.9).

3.5 Presenting signs among the study population:

Fourteen patients were found to have ptosis (14.4%) partly due to lid oedema and partly mechanical due to giant papillae.

Some patients had signs of palpepral VKC (papillary hypertrophy 68% and giant papillae 16.5%), while others had signs of the limbal VKC, in the form of limbitis 65.9% and Trantas' dots 35%. Both signs may coexist in some cases. Small number of patients had corneal involvement; corneal plaque (14 patients), corneal opacity (7 patients) and SPK (6 patients) table (3.10).

3.5.1 Grading of signs among the study population

3.5.1.1 Base line signs

As demonstrated in table (3.11) congestion (hyperaemia) was mild in 31 patients (32%), moderate in 32 patients (33%) and severe in 32 patients (33%). Severe limbitis was detected in 10 patients (10.3%) and only one patient had severe Trantas' dots.

3.5.1.2 1st visit (after two weeks)

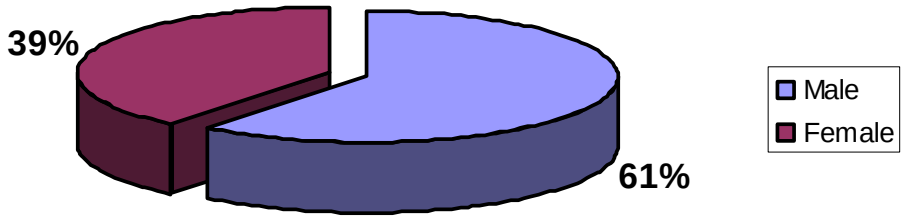
The severity of signs (hyperaemia, limbitis and Trantas' dots) was significantly reduced in both the study and control group (p value<0.05). SPK was the only exception in which there was no significant change (tables 3.12, 3.13, 3.14, 3.15).

3.5.1.3 2nd visit (after four weeks)

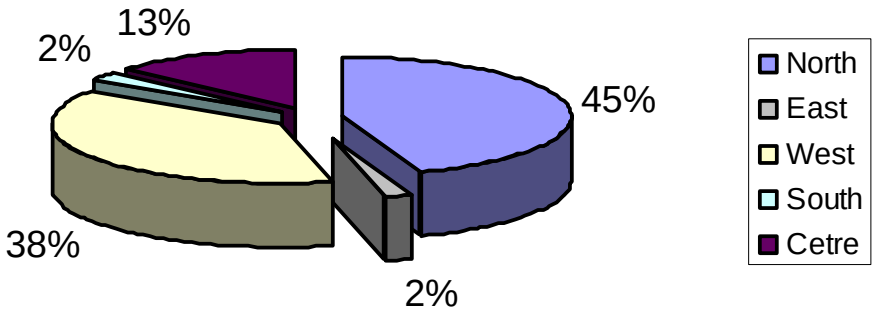
Hyperaemia and limbitis showed further significant improvement among the study group. Regarding Trantas’ dots there was no change from the results that obtained in the first follow up visit.

In the control group the signs were unchanged (tables 3.12, 3.13, 3.14, 3.15).

figure(3.1)
Sex distribution of the study population



figure(3.2)
Distribution of the study population according to residence



figure(3.3)
Distribution of the study sample according the past ocular history of VKC

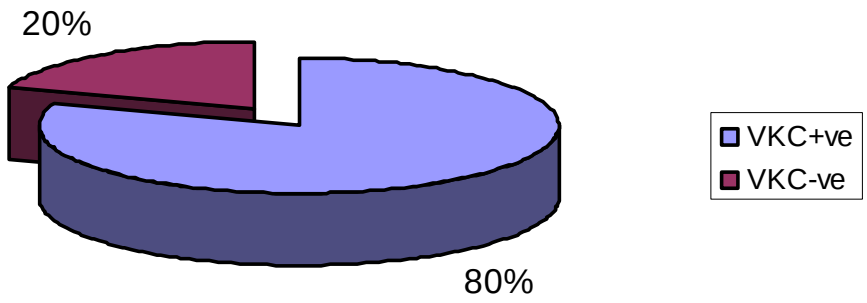


Table (3.1)

Age &sex distribution among the study population

Age in year	Male	Female	Total	
			Frequency	Percent
< 5	14	7	21	21.65%
5-9	12	10	22	22.68%
10-14	16	8	24	24.75%
15-19	15	8	23	23.71%
20-24	1	2	3	3.09%
25-29	0	3	3	3.09%
> 30	1	0	1	1.03%
Total	59	38	97	100%

Table (3. 2)
Family history of VKC or other atopy among the study population

Family History	VKC		Other atopy	
	Frequency	Percent	Frequency	Percent
Positive	35	36%	22	22.7%
Negative	62	64%	75	77.3%
Total	97	100%	97	100%

Table (3.3)
Presenting complaints (symptoms) of the study population

Symptom	Grading								Total	
	No		Mild		Moderate		Severe			
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Itching	1	1.03%	3	3.09%	13	13.40%	80	82.47%	96	98.97%
Photophobia	39	40.21%	10	10.31%	16	16.49%	32	32.99%	58	59.79%
Lacrimation	27	27.83%	14	14.44%	15	15.46%	41	42.27%	70	72.17%
Discharge	25	25.80%	20	20.60%	19	19.58%	33	34.02%	72	74.20%
Foreign body sensation	29	37.66%	6	7.79%	10	12.99%	32	41.56%	48	62.34%
Discoloration	9	9.30%	11	11.30%	13	13.40%	64	66.00%	88	90.70%

Table (3.4)
Grading of itching among study population

Itching	1st day				1st visit				2nd visit			
	Study group		Control group		Study group		Control group		Study group		Control group	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
No	0	0%	1	3.45%	32	47.06%	9	31.03%	38	55.88%	2	6.90%
Mild	3	4.41%	0	0%	29	42.65%	14	48.28%	21	30.88%	16	55.17%
Moderate	10	14.71%	3	10.34%	5	7.35%	5	17.24%	2	2.95%	6	20.69%
Severe	55	80.88%	25	86.21%	2	2.94%	1	3.45%	7	10.29%	5	17.24%
Total	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**

Table (3. 5)
Grading of Photophobia among study population

Photophobia	1st day				1st visit				2nd visit			
	Study group		Control group		Study group		Control group		Study group		Control group	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
No	38	55.88%	13	44.83%	53	77.94%	19	65.52%	60	88.23%	20	68.96%
Mild	21	30.88%	2	6.90%	8	11.76%	8	27.58%	4	5.88%	7	24.14%
Moderate	2	2.94%	6	20.69%	6	8.82%	1	3.45%	3	4.41%	2	6.90%
Severe	7	10.30%	8	27.58%	1	1.48%	1	3.45%	1	1.48%	0	0%
Total	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**

Table (3.6)

Grading of Lacrimation among study population

Lacrimation	1st day				1st visit				2nd visit			
	Study group		Control group		Study group		Control group		Study group		Control group	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
No	20	29.41%	7	24.14%	47	69.12%	19	65.52%	51	75.00%	12	41.38%
Mild	9	13.23%	5	17.24%	17	25.00%	5	17.24%	12	17.65%	11	37.93%
Moderate	12	17.65%	3	10.34%	2	2.94%	5	17.24%	2	2.94%	6	20.69%
Severe	27	39.71%	14	48.28%	2	2.94%	0	0%	3	4.41%	0	0%
Total	68	100%	29	100%	68	100%	29	100%	68	100%	29	100%

Table (3.7)
Grading of Discharge among study population

Discharge	1st day				1st visit				2nd visit			
	Study group		Control group		Study group		Control group		Study group		Control group	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
No	15	22.05%	10	34.48%	48	70.58%	20	68.96%	56	82.35%	16	55.17%
Mild	14	20.59%	6	20.69%	17	25.00%	6	20.69%	6	8.82%	10	34.48%
Moderate	14	20.59%	5	17.24%	2	2.94%	2	6.90%	3	4.41%	1	3.45%
Severe	25	36.77%	8	27.59%	1	1.48%	1	3.45%	3	4.41%	2	6.90%
Total	68	100%	29	100%	68	100%	29	100%	68	100%	29	100%

Table (3. 8)
Grading of Foreign body sensation among study population

Foreign body sensation	1st day				1st visit				2nd visit			
	Study group		Control group		Study group		Control group		Study group		Control group	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
No	**18**	**26.47%**	**11**	**37.93%**	**30**	**44.12%**	**19**	**65.52%**	**36**	**52.94%**	**18**	**62.07%**
Mild	**5**	**7.35%**	**1**	**3.45%**	**10**	**14.70%**	**3**	**10.34%**	**11**	**16.17%**	**4**	**13.80%**
Moderate	**6**	**8.83%**	**4**	**13.79%**	**7**	**10.30%**	**5**	**17.24%**	**1**	**1.48%**	**3**	**10.34%**
Severe	**20**	**29.41%**	**12**	**41.38%**	**2**	**2.94%**	**1**	**3.45%**	**1**	**1.48%**	**3**	**10.34%**
Non	**19**	**27.94%**	**1**	**3.45%**	**19**	**27.94%**	**1**	**3.45%**	**19**	**27.94%**	**1**	**3.45%**
Total	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**

Table (3. 9)
Grading of redness or Discoloration among study population

Discoloration or redness	1st day				1st visit				2nd visit			
	Study group		Control group		Study group		Control group		Study group		Control group	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
No	**4**	**5.88%**	**5**	**17.24%**	**29**	**42.65%**	**12**	**41.38%**	**42**	**61.76%**	**7**	**24.13%**
Mild	**9**	**13.24%**	**2**	**6.90%**	**27**	**39.71%**	**11**	**37.92%**	**18**	**26.48%**	**13**	**44.83%**
Moderate	**7**	**10.30%**	**6**	**20.69%**	**8**	**11.76%**	**4**	**13.80%**	**3**	**4.41%**	**4**	**13.80%**
Severe	**48**	**70.58%**	**16**	**55.17%**	**4**	**5.88%**	**2**	**6.90%**	**5**	**7.35%**	**5**	**17.24%**
Total	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**

Table (3.10)
Presenting signs among study population

Sign	Frequency	Percent
Ptosis	14	14.43%
Lid oedema	21	21.64%
Blepharitis	2	2.06%
Hyperaemia	95	97.93%
Limbitis	64	65.97%
Trantas' spot	34	35.05%
Superficial punctate keratitis	6	6.18%
Papillary Hypertrophy	66	68.04%
Giant Papillae	16	16.49%
Corneal Scar	5	5.15%
Pannus	11	11.34%
Corneal plaque	14	14.43%
Corneal opacity	7	7.21%
Keratoconnus	3	3.09%

Table (3. 11)
Baseline grading of signs among the study population

Sign	Grading								Total	
	No		Mild		Moderate		Severe			
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Hyperemia	2	2.10%	31	31.90%	32	33%	32	33%	95	97.9%
Limbitis	33	34%	24	24.75%	30	30.94%	10	10.31%	64	66.00%
Trantas' spot	63	64.95%	19	19.59%	14	14.43%	1	1.03%	34	35.05%
Superficial punctate keratitis	91	93.82%	3	3.09%	3	3.09%	0	0%	6	6.18%

Table (3.12)
Grading of Hyperaemia among study population

Hyperemia	1st day				1st visit				2nd visit			
	Study group		Control group		Study group		Control group		Study group		Control group	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
No	**1**	**1.47%**	**1**	**3.45%**	**25**	**36.76%**	**10**	**34.48%**	**48**	**70.59%**	**6**	**20.69%**
Mild	**24**	**35.29%**	**7**	**24.14%**	**36**	**52.95%**	**16**	**55.17%**	**16**	**23.53%**	**16**	**55.17%**
Moderate	**21**	**30.88%**	**11**	**37.93%**	**4**	**5.88%**	**3**	**10.35%**	**1**	**1.47%**	**7**	**24.14%**
Severe	**22**	**32.36%**	**10**	**34.48%**	**3**	**4.41%**	**0**	**0%**	**3**	**4.41%**	**0**	**0%**
Total	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**

Table (3.13)
Grading of Limbitis among study population

Limbitis	1st day				1st visit				2nd visit			
	Study group		Control group		Study group		Control group		Study group		Control group	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
No	**23**	**33.83%**	**10**	**34.48%**	**40**	**58.82%**	**17**	**58.62%**	**57**	**83.82%**	**13**	**44.83%**
Mild	**16**	**23.53%**	**8**	**27.59%**	**23**	**33.83%**	**8**	**27.59%**	**8**	**11.77%**	**12**	**41.38%**
Moderate	**22**	**32.35%**	**8**	**27.59%**	**3**	**4.41%**	**4**	**13.79%**	**3**	**4.41%**	**4**	**13.79%**
Severe	**7**	**10.29%**	**3**	**10.34%**	**2**	**2.94%**	**0**	**0%**	**0**	**0%**	**0**	**0%**
Total	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**

Table (3.14)
Grading of Trantas' spot among study population

Trantas' spot	1st day				1st visit				2nd visit			
	Study group		Control group		Study group		Control group		Study group		Control group	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
No	**45**	**66.18%**	**18**	**62.07%**	**56**	**82.35%**	**21**	**72.41%**	**62**	**91.18%**	**21**	**72.41%**
Mild	**12**	**17.65%**	**7**	**24.14%**	**10**	**14.71%**	**7**	**24.14%**	**4**	**5.88%**	**8**	**27.59%**
Moderate	**11**	**16.17%**	**3**	**10.34%**	**2**	**2.94%**	**1**	**3.45%**	**2**	**2.94%**	**0**	**0%**
Severe	**0**	**0%**	**1**	**3.45%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**
Total	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**

Table (3.15)
Grading of Superficial punctate keratitis among study population

SPK	1st day				1st visit				2nd visit			
	Study group		Control group		Study group		Control group		Study group		Control group	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
No	**66**	**97.06%**	**25**	**86.21%**	**66**	**97.06%**	**26**	**89.66%**	**67**	**98.53%**	**26**	**89.66%**
Mild	**0**	**0%**	**3**	**10.34%**	**2**	**2.94%**	**3**	**10.34%**	**1**	**1.47%**	**3**	**10.34%**
Moderate	**2**	**2.94%**	**1**	**3.45%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**
Severe	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**	**0**	**0%**
Total	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**	**68**	**100%**	**29**	**100%**

CHAPTER FOUR

4.1 Discussion

Most of the patients in our study were below the age of 20 years. From this large group about 67 children were affected, this is confirmed by what was mentioned in the literature that VKC is usually a disease of children [52] which begins in prepubertal years and lasts for 5 – 10 years [53].

The majority of patients in our study were males (60.8%). The disease occurs more often in boys than in girls. This was also mentioned in literature [18.19.21] and goes with our findings. While Duane showed that only one series pointed out to a female preponderance [5].

All patients included in this study were living in Khartoum state but originally most of them (44.3%) were from Northern Sudan, a state known by its dry & hot weather. The disease is more common in tropics and Sudan is one of the tropical countries. This disease is almost always more sever during the spring, summer & fall then in winter [53].

In Sudan the severity is usually due to dusty and sandy winds, and grass pollen sensitivity in transitional period between winter and autumn.

The majority of patients had past history of VKC and this indicates the recurrence of the disease with a strong history of allergies.

It is known as seasonal or warm weather conjunctivitis, the identification of specific allergens is still a mystery [53].

It is a hypersensitivity reaction to exogenous allergens and is mediated by IgE as indicated by the accompanying easinophilia [18].

Family history of atopy in patients with VKC was mentioned by Kanski, Duane and Yanof[4,5,6]. This confirms our finding. One third of the patients in our study had a family history of VKC and one fourth had a family history of atopy.

The main presenting symptom among our study population was itching; it has been described as the main symptom of VKC [4,18,20].

It is mentioned in the literature that the chief complaint of VKC are photophobia, lacrimation and mucoid discharge being the second after itching, in our study redness or discoloration was the second presenting complaint and this may be explained by two factors: a racial factor, most of the Sudanese people are black skin indicating more pigmentation and a climatic factor where most of the year weather in Sudan is hot and dry with dusty winds

which irritates the eye making it red. The claim that discoloration is changing according to the severity of the disease may be due to the overlapping by redness.

In the first follow up, all patients (study and control groups) showed significant improvement of their previous complaints. This improvement is mostly due to the anti-inflammatory effects of steroids. Sodium cromoglycate has no direct antihistaminic effect and must be used prophylacticaly for several weeks to be effective [18].

In the second follow up when steroids have been stopped and treatment was continued only with either sodium cromoglycate or placebo, the study group showed continuous stationary improvement as regarding itching, lacrimation and discharge, the chief symptoms of VKC. Further significant improvement occurs in photophobia, foreign body sensation and redness.

This result can be attributed to mast cell stabilization effect of sodium cromoglycate as a prophylactic drug.

Among the control group itching, redness and lacrimation were getting worse. While photophobia, F.B. sensation and discharge were remain at the same level. This may be explained by the soothing and washing effect of tears naturale.

This confirms what other studies concluded, that sodium cromoglycate is more effective in reliving symptoms of VKC than placebo [40, 41, 45].

The presenting signs:

The first examination of the study population revealed that hyperaemia was the most common presenting sign followed by papillary hypertrophy, limbitis and Trantas' dots.

Hyperaemia is a characteristic finding in both palpebral & bulbar or limbal VKC and this goes with our findings that hyperemia was detected in about 98% of our patients.

Papillary hypertrophy and limbitis occurred nearly by the same percentage. This may be explained by that in the palpebral VKC, papillary hypotrophy is a characteristic finding while in bulbar or limbal VKC limbitis is the characteristic sign and both are present in the combined type of VKC.

Trantas' dots which is a pathognomonic sign of the bulbar type of VKC was detected in about one third of the study population. This finding is confirmed by what was mentioned in the literature that limbal VKC is more common in black patients [4]

.

Corneal signs are much less compared with palpebral & bulbar signs. Among the corneal signs, corneal plaque was the commonest. It is known that the plaque is usually caused by epithelial macro erosions, in which the base becomes coated with layers of altered exudation which can not be wetted by tears and resist re-epithelization .This may explain why its percentage is high among the corneal findings.

SPK was detected in about 6% of all the study population and accounted for about 15% only among the corneal signs. Although it was known to be the commonest corneal sign in VKC, in our study it was the 3rd sign after plaque and corneal opacity. This may be explained by the fact that both plaque and corneal opacities occurred as a complication of epithelial macro erosion.

The first follow up:

As regarding the signs of VKC among our study population there was a significant improvement in the presenting signs especially hyperaemia, limbitis and Trantas' spot. This improvement was with no doubt due to the effect of steroids.

As regarding corneal signs especially SPK there was no considerable improvement, this may be explained by the fact that

none of the corneal lesions respond well to standard treatment [53] or this may be because of the small number of patients with corneal manifestations in our study. Evaluation of this finding needs more patients with corneal manifestations. These findings were the same for both study and control groups.

The second follow up:

Among the study group there was marked improvement of VKC signs namely hyperaemia, limbitis and Trantas' spot especially in the moderate and severe cases. This signifies the role of sodium cromoglycate .Topical Sodium cromoglycate is a useful prophylactic agent in moderate to severe cases of VKC [53]. Among the control group the signs were slightly improved "not significant" from the first day of examination up to the second visit, this may be due to the prolong effect of topical steroids.

4.2 Conclusions

1. Sodium cromoglycate is a useful prophylactic agent in the treatment of VKC.

2. Steroids were effective in eliminating severe symptoms and signs of VKC.

3.3 Recommendations

1. More scientific researches and studies are required to identify the specific allergen or allergens which is/are still a mystery cause of VKC.
2. Discourage the use of the steroids in the treatment of VKC unless it is necessary and for short time.
3. Encourage the use of sodium cromoglycate and other mast cell stabilizers as it is proved to be effective as a prophylactic agent in the treatment of VKC.
4. Complementary study is needed to evaluate the effect of sodium cromoglycate in decreasing the severity of symptoms and signs of VKC prior to the time of exacerbation.
5. Advice patients of VKC to:

- Use sunglasses and avoid heat and dust
- Sleeping and if possible working in a cool air-conditioned rooms
- Move to cool moist climate if possible.

These advices can keep the patients reasonably comfortable.

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APPENDIX

EFFECT OF SODIUM CROMOGLYCATE IN SUDANESE PATIENTS

WITH VERNAL KERATOCONJUNCTIVITIS

QUESTIONNAIRE

PERSONAL DATA

CASE NO: ----------

NAME: ----------AGE----------GENDER---------- RESIDENCE -------

FAMILY HISTORY: ---------- PAST OCCULAR HISTORY----------

OCCULAR MEDICATION----------

OTHER SENSITIVITY: ----------

SYSTEMIC DISESAE

ASTHMA [____]
ECZEMA [____]
OTHERS [____]

CHIEF COMPLAINTS
SYMPTOMS

ITCHING	**IST DAY**	**2ND WEEK**	**4TH WEEK**
o **NONE=0** o **MILD=1** o **MODERATE=2** o **SEVERE=3**			
PHOTOPHOBIA			
o **NONE=0** o **MILD=1** o **MODERATE=2** o **SEVERE=3**			
LACRIMATION			
o **NONE=0** o **MILD=1** o **MODERATE=2** o **SEVERE=3**			
DISCHARGE			
o **NONE=0** o **MILD=1** o **MODERATE=2** o **SEVERE=3**			
F.B SENSATION			
o **NONE=0** o **MILD=1** o **MODERATE=2** o **SEVERE=3**			
REDNESS OR BROWN DISCOLORATION			
o **NONE=0** o **MILD=1** o **MODERATE=2** o **SEVERE=3**			

EXAMINATION

VA----------R----------L---------- REFRACTION----------

VA/CORRECTED----------R---------L---------- OCCULAR MOVEMENT----------

	IST DAY	2ND WEEK	4TH WEEK
EYE LID			
PTOSIS **OEDEMA** **ENTROPION** **ECZEMA**			
LID MARGIN			
MADAROSIS **TRICHIASIS** **BLEPHARITIS**			
PALPEBERALCONJUNCTIVA			
HYPERAEMIA **PAPILARY HYPERTROPHY** **GIANT PAPILLAE (COBBLE STONE)** **SCAR**			
BULBAR CONJUNCTIVA			
HYPERAEMIA **CHEMOSIS** **DISCOLORATION**			
LIMBUS			
GELATENOUS MATERIAL **TRANTAS' SPOT**			
CORNEA			
S.P.K **PANNUS** **MACRO EROSION** **CORNEAL ULCER** **CORNEAL PLAQUE** **SUP.VASCULARIZATION** **DEEP VASCULARIZATION** **CORNEAL OPACITY** **KERATOCONUS**			
EPISCLERA			
SCLERA			
ANTERIOR CHAMBER			
IRIS			
LENS			
RETINA			

TREATMENT SODIUM CROMOGLYCATE [____] [____]
STEROIDS [____] [____]
TEARS NATURALE [____] [____]