THERAPEUTIC RESPONSES IN VERNAL KERATOCONJUNCTIVITIS

A DISSERTATION FOR THE DEGREE OF MASTER OF MEDICINE (M.MED) IN OPHTHALMOLOGY OF THE UNIVERSITY OF DAR ES SALAAM

BY

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ABSTRACT

This was a single-blind placebo controlled study conducted at the Muhimbili Medical Centre between March 1989 and May 1990. It involved 60 patients with vernal keratoconjunctivitis, an ocular allergic inflammatory condition of world-wide distribution, involving mainly the conjunctiva and the cornea.

The objective of the study was to find out the most efficacious therapeutic method in alleviating the signs and symptoms of the disease in our environment since different authorities from different parts of the wold have claimed success using different therapeutic methods.

The patients were randomly selected into four (4) groups, each subjected to a different therapeutic method. The therapy groups were: (i) placebo (ii) cryotherapy (iii) oral aspirin and (vi) steroid-antibiotic. The intensity of signs and symptoms were graded using a prepared score table. The higher the score, the more intense the disease was. After initial assessment, the patients were subjected to their respective therapies and signs and symptoms assessed and graded first weekly then twice weekly.

The mean follow up period was 4 weeks. The odds-ratio method was used to assess the effectivity of the drugs with respect to placebo. Cryotherapy was found to be the most effective therapeutic method in alleviating signs and symptoms of the disease compared to other drugs used.

A recommendation is made that patients with intractable vernal keratoconjunctivitis should be subjected to cryotherapy for relief of signs and symptoms.

DECLARATION

I hereby declare that this dissertation is my own original work and has not been submitted for a degree or diploma in any other university.

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INTRODUCTION

Vernal Keratoconjunctivitis is an ocular condition with symptoms of itching, tearing photophobia and a stringy mucoid discharge from the eyes. It is associated with inflammation of both the bulbar and palpebral conjunctiva and sometimes corneal manifestations like corneal ulcers and keratoconus.

Though the dangers of visual loss are minimal in this condition, the persistent itching and tearing is a source of great discomfort to the victim of the disease, so much so that very often medical advice is sought.

There is no single specific treatment so far for this condition, though various authors have reported success in abolition of the symptoms with steroids (Neumann, 1958; Dahan et al., 1983), sodium cromoglycate (Easty et al., 1972; Forster, 1988) and cryotherapy (Amoils, 1975; Mtanda and Sangawe, 1983). Aspirin has once been tried in this condition with success (Abelson et al., 1983).

There is a need to establish the efficacy of various reported therapies in this condition, in order to come out with the best alternative in our environment. This is possible in a placebo controlled, blind study comparing the various methods simultaneously. The resulting evidence may help us in managing the scores of patients with this condition with the best available medical or surgical alternative.

REVIEW OF LITERATURE

THE CONJUNCTIVA

1. ANATOMICAL CONSIDERATIONS:

A. Gross anatomy:

The conjunctiva is a thin, transparent mucous membrane that covers the posterior surface of the lids, and the anterior surface of the sclera, on the eyeball. It is continuous with the skin at the lid margins (mucocutaneous junction) and with corneal epithelium at the limbus.

For the purposes of description, it is divided into three portions; the bulbar portion, palpebral portion and the fornix (Wolf E., 1968).

I) The bulbar conjunctiva:

This is a thin and transparent membrane, covering the anterior portion of the sclera, through which it clearly shows. It is loosely bound by loose areolar tissue to the underlying Tenons capsule and the sclera until about 3 mm from the limbus where it is more closely bound to them. At this point, the conjunctiva is slightly raised by a small ridge. This is known as the limbal conjunctiva, and the raised edge becomes more apparent in vernal conjunctivitis and other inflammatory conditions.

At the limbus, the conjunctiva, Tenons capsule and sclera are all fused into a dense tissue. The bulbar conjunctiva is in continuity with the corneal epithelium and often diseases involving the conjunctiva may spread to involve the cornea and vice versa (Morehead R.P., 1965).

II) **The Palpebral conjunctiva:**

This may be subdivided into the marginal zone, tarsal zone and orbital zone.

The marginal zone: This is a 2 mm transition zone between the skin of the eyelids and the conjunctiva. It communicates with the nasal cavity through the lacrimal puncta which open into it. Diseases of the nasal cavity may therefore spread into the conjunctiva and vice versa.

The tarsal zone: is thin and very much adherent to the underlying superior tarsal plate. It is well vascularized, giving it a reddish or pinkish colour.

The orbital zone: extends between the superior edge of the tarsal plate and the fornices. This zone is loosely held to the underlying tissues, and is thrown into horizontal folds. The area just above the superior tarsal plate is thrown into shallow grooves resembling papillae (Stieda's plateaux and grooves). These are not true papillae though.

III) **The fornix conjunctivae:**

This is loosely bound conjunctiva lining the fornices; it is adherent to loose fibrous tissue, which is derived from the fascial expansions of the recti muscles and the levator palpebral superioris. It is divided into superior, lateral, medial and inferior fornices for descriptive purposes.

The fornix conjunctiva contains the glands of Krause and also forms an insertion for the levator palpebral superioris through fibrous extensions. These extensions can deepen the fornices when the muscles contract.

B. **Microscopic anatomy:**

The conjunctiva, is a mucous membrane which consists of two layers:- (i) the epithelium

(ii) the substantia propria.

I) **The Epithelium:**

The structure of the epithelium differs from one part of the eye to the other and also according to age due to pathological changes taking place from time to time (Wolfe, 1968).

(a) **Lid margins:**

The free margin of the lids are covered by stratified squamous cell epithelium which is keratinised. This ends abruptly at the mucocutaneous junction where the epithelium of the conjunctiva starts.

(b) **Mucocutaneous junction:**

Epithelium consists of 5 layers of non-keratinised squamous epithelium with top layers retaining their nuclei. The next layer consists of polyhedral cells while the deepest layer consists of high cylindrical cells. Just beyond the mucocutaneous junction, mucous providing unicellular glands the goblet cells are found in moderate amounts.

(c) **The tarsal conjunctiva:**

Upper eyelids:

The epithelium consists of two layers:- Superficial layers consisting of tall cylindrical cells with oval nuclei near the base of the cells axes, at right angles to the surface, and a deeper layer consisting of cubical cells with oval nuclei, with their long axes parallel to the surface.

Lower eyelid:

Has 3-4 layers of cells, with cubical basal cells, followed by polygonal cells, superficial to which are elongated, wedge-shaped cells and the most superficial are cone-shaped.

(d) **The fornix:**

Structure is like the upper eyelid epithelium except that a third layer of polyhedral cells is inserted between the superficial cylindrical layer and the deep cubical cell layer.

(e) **The limbus:**

The conjunctival epithelium at the limbus is thick, having a layer of 10 to 15 cells thickness with absence of goblet cells (Hogan M.J. et al., 1971). The basal layer consists of a single layer of cylindrical cells, followed by several layers of polygonal cells, and superficially, one or two layers of flattened cells.

II) **The Stroma:**

Consists of two portions:

a) the adenoid layer (superficial)

b) the fibrous layer (deeper)

(a) **The adenoid layer:**

Absent at birth, it is first formed 3 to 4 months post delivery. It consists of a fine connective tissue reticulum into which lies lymphocytes. It is not found in

the marginal conjunctiva.

(b) **Fibrous layer:**

Lies deep to the adenoid layer, and is thicker. It is almost absent over the tarsus. In it are found the vessels and nerves to the conjunctiva. Also present in the stroma are fibroblasts, macrophages, mast cells, polymorphonuclear, leukocytes, eosinophils and plasma cells (Wedel et al., 1971).

Blood supply:

Blood supply is from three sources:

Peripheral arterial arcades:- formed from the lacrimal artery, and the supra-orbital artery, supply most of the tarsal, fornix and bulbar conjunctiva. The vessels move with the conjunctiva.

Marginal arterial arcades:- Mainly supply the marginal conjunctiva and send anastomotic branches, to the peripheral arcade.

Anterior ciliary artery:- Branches of the muscular arteries to the recti pass at a deeper plane, and at 4 mm from the limbus, pierce the sclera to form the major arterial circle of the iris. Branches of these arteries also anastomose with each other to form a pericorneal plexus, which forms the "ciliary injection" in diseases of the iris, ciliary body and deeper portions of the cornea. These vessels do not move with the conjunctiva.

The venous drainage usually follows the corresponding arteries draining into the respective palpebral veins, muscular veins and finally ophthalmic veins into the carvenous sinus.

Lymphatic drainage:

The lymphatic vessels draining the conjunctiva are found in the fibrous portion of the stroma. Those on the medial side drain into the sub-mandibular lymph nodes, and those on the lateral side drain into the parotid nodes.

2. PATHOLOGICAL CHANGES IN CONJUNCTIVAL INFLAMMATIONS:

Pathological changes in the conjunctiva differ in acute inflammations as compared to chronic inflammations.

(A) Acute inflammations:

In acute inflammations the changes include exudation, chemosis (oedema), inflammatory membranes and ulceration.

I) Exudation:

Exudation is a feature of all types of acute conjunctival inflammations. The exudation may be flaky and amorphous in bacterial keratoconjunctivitis or stringy in the case of vernal keratoconjunctivitis (Vaughan, D-1980). The type of cellular exudates are characteristic of the type of conjunctivitis (Yanoff M., 1975).

Neutrophils: Characteristic of bacterial conjunctivitis.

Eosinophil: Characteristics of allergic conjunctivitis, an example being vernal catarrh.

Basophils: Characteristic of allergic conjunctivitis.

Mononuclear cells:

Characteristic of tuberculosis, rubella and Herpes.

The inflammatory cells migrate from the conjunctival stroma through the epithelium to the surface. They then combine with fibrin and with the mucous produced by the conjunctival goblet cells to form the conjunctival exudate (Vaughan, D-1977).

II) **Ulceration:**

Loss of epithelium with or without loss of subepithelial tissue associated with an inflammatory cellular infiltrate may occur during the course of acute conjunctivitis.

III) **Chemosis:**

This is oedema of the conjunctiva characterized by a translucent swelling of the membrane. It is less prominent in the tarsal conjunctiva where the conjunctiva is tightly bound to the underlying tarsus, and is more prominent in the bulbar conjunctiva where massive exudation may occur, giving a ballooning out picture of the conjunctiva which may even protrude through the eyelids. The cause may be an acute inflammation or vascular stasis all giving rise to increased permeability of the conjunctival vessels (Duke-Elder, 1965). The oedema in chemosis actually involves the stromal portion of the conjunctiva.

IV) **Inflammatory membranes:**

(a) True membrane:

A true membrane consists of an exudate of fibrin and cellular debris firmly attached to the underlying epithelium by fibrin. When the true membrane is removed, the epithelium is also stripped off leaving a raw bleeding surface. This may be seen in epidemic keratoconjunctivitis, Diphtherial infections, S-J syndrome, and staph. aureus. infections.

(b) Pseudomembrane:

This consist of a loose fibrin-cellular debris, not adherent to the underlying epithelium and from which it is stripped off easily.

(B) **Chronic inflammations:**

Several changes may take place in chronic inflammations of the conjunctiva and these include papillary hypertrophy, follicular formation, keratinisation and granuloma formation.

I) **Papillary hypertrophy:**

This is basically a vascular response with secondary inflammatory cell infiltration. The conjunctiva is thrown into folds or projections due to oedematous sub-epithelial tissue infiltration. These folds/projections contain a core of vessels and the sub-epithelial tissue is often infiltrated with chronic inflammatory cells; lymphocytes and plasma cells predominating. The epithelium covering the projections is hyperplastic.

Upper tarsus papillae are typical of vernal keratoconjunctivitis where they are clinically large, flat-topped, polygonal and milky in colour (Duke Elder, 1965). Limbal papillae may also occur along the interpalpebral space where they appear as gelatinous infiltrates that may encroach on the cornea. Giant papillary hypertrophy, histologically similar to that found in vernal keratoconjunctivitis has also been found in some patient wearing soft or hard contact lenses (Allansmith et al., 1977) and also in patients with ocular prostheses (Srinivasan et al., 1979).

II) **Follicular formation:**

This consists of focal lymphoid hyperplasia within the adenoid layer of the conjunctiva, usually containing a germinal centre. Follicles may be found in the tarsus in diseases of chlamydial (eg trachoma) or viral origin and in toxic conjunctivitis. Follicles in the fornices and tarsal margin are of limited diagnostic value. (Vaughan, 1980).

III) **Keratinisation:**

With chronic exposure of the conjunctiva or avitaminosis. A (Xerophthalmia) the superficial conjunctiva cells become flat and are desquamated, "prickle" cells appear, the conjunctiva epithelium becomes keratinised thus assuming the characteristics of skin except hair follicles and sebaceous glands.

IV) **Granuloma formation** may occur in chronic granulomatous conditions eg sarcoidosis.

V) In chronic conjunctival irritation, the conjunctiva may undergo epithelial and goblet cell proliferation, and these may cause infoldings within the conjunctival architecture to resemble glandular structures in tissue section - pseudoglands.

3. HYPERSENSITIVITY REACTIONS OF THE CONJUNCTIVA:

The conjunctiva being in an exposed surface, is vulnerable to invasion by a wide range of microorganisms, and also comes into contact with numerous non infective allergenic substances either accidentally, or by design. Immunological mechanisms have evolved, having a protective effect from injurious processes of invading organisms. When, however, the immunologic response to extraneous antigens has harmful effects to the host tissue, the reaction is known as allergy or hypersensitivity (Rahi & Garner, 1976).

In the conjunctiva, virtually all types of hypersensitivity reaction may be recognised. Friedlander and Allansmith (1975) have summarised the hypersensitivity reactions in the eye as follows:

Type I hypersensitivity:

This results when an antigen combines with a mast cell-bound homocytotropic antibody with the subsequent release of vasoactive substances e.g. histamines, bradykinins, 5HT,

prostaglandins and eosinophil chemotactic factor. Examples of such hypersensitivity are vernal kerato-conjunctivitis, acute allergic conjunctivitis and atopic eczema.

Type II hypersensitivity:

A cytotoxic antibody is directed against a specific type of cell or tissue, rendering it more susceptible to destruction, examples being pemphigus and pemphigoid.

Type III hypersensitivity:

Involves the formation of immune complexes which may localise in organs and trigger an inflammatory reaction. In the conjunctiva, such reactions are exemplified by conditions like erythema multiforme (Stephen-Johnson Syndrome) and erythema nodosum.

Type IV hypersensitivity (Delayed hypersensitivity):

In this type of hypersensitivity reactions, there is interaction of a specific antigen with sensitised lymphocytes. These lymphocytes produce lymphokines which cause among other things, cytotoxicity.

Vernal keratoconjunctivitis, a type I hypersensitivity reaction involving the conjunctivae and cornea will be discussed in details, regarding the pathophysiology, pathogenesis and therapeutic alternatives.

4. VERNAL KERATOCONJUNCTIVITIS:

A) Introduction:

This is a seasonal recurrent bilateral inflammation of the conjunctiva, (sometimes with involvement of the cornea) characterised by cobblestone papillae on the tarsal conjunctiva, and a discrete or confluent papillary hypertrophy on the limbal conjunctiva, with major symptoms of itching, photophobia, and tearing (Allansmith, 1982).

The synonyms of this condition are spring catarrh and vernal catarrh. It was first described by Arlt in 1846, who noted gelatinous limbal swelling in three young patients (Buckley, 1981). In 1876, it received the name spring catarrh from Saemisch, who observed and insisted its periodicity, it being worse in spring. A marked contribution to the extent of the disease was by Trantas (1910) who first gave notice to corneal complications Trantas spots (Duke Elder, 1965). Todate, the disease is still being extensively studied.

It is generally agreed, that vernal catarrh is a disease of the young (5-20 yrs) and also that it affects males more than females (Allansmith, 1981; Dahan et al., 1983; Foster et al., 1988), although some authors suggest that the sex ratio may be the same (Duke Elder, 1965; Sandford-Smith, 1978).

The disease is more prevalent in the tropics (Sandford-Smith, 1978; Dahan et al., 1982) and the Mediterranean (Neumann, 1958; Baryshak et al. 1982) while it is of relatively low incidence in temperate climates.

There are seasonal variations of the disease in temperate

countries, it being worse in the late spring, hence the name, spring catarrh. In the tropics however, where the temperatures are persistently high, there are no seasonal variations in the clinical picture of the disease (Sandford-Smith, 1978).

Some authors also report clinical variations of the disease picture in the different races, and blacks are said to have mostly the limbal type while whites have the palpebral type (Dahan et al., 1983).

The symptoms of the disease may vary from very mild, to very severe; generally comprising of itching which may be very persistent and intolerable, a burning sensation, foreign body sensation, tearing and photophobia. (Duke Elder, 1965).

The diagnostic signs are thick stringly mucous discharge, a giant cobblestone papillary reaction of the upper tarsal conjunctiva, papillary changes of the bulbar conjunctiva and sometimes corneal complications.

Clinically, the disease has two forms the palpebral and the limbal, which may occur either singly or together with one predominating (Allansmith, 1982). The palpebral form affects the tarsal conjunctiva of the upper lid, while lower lid changes may be slight or absent. The changes in the upper tarsal conjunctiva first include a mild papillary hypertrophy, later developing to hard discrete papillae of various sizes which eventually may form giant, flat-topped crowded cobblestone papillae. The most affected area is usually the superior border of the tarsal plate. A milky veils that usually overlies the cobblestone papillae can be easily removed if a cotton wool applicator is passed over it.

The limbal form consists of a thickened, broad, gelatinous

opacification of the upper limbus. Occasionally the changes mentioned may affect the whole limbus but still are most marked in the upper limbus. Nodules may appear on top of the thickened limbus within which, chalk-like whitish dots may be seen. These are the Horner-Trantas dots, composed of concretions of eosinophil and are pathognomonic of the disease. They may appear at any stage.

Corneal complications are a cause of distressing symptoms like pain, photophobia and tearing, and these are usually associated with the palpebral form of the disease (Neumann, 1958; Sandford-Smith, 1978) but even in untreated cases the danger for permanent visual loss appears to be slight. (Sandford-Smith, 1978).

Corneal changes were first described by Trantas (1910) who described a variety of corneal changes some of which still bear his name (Horner-Trantas dots). An extensive study was done by Neumann (1958) who noted their response to steroid therapy. Buckley (1981 describes the corneal complications as punctate epithelial keratitis, epithelial micro-erosions, plaque, subepithelial scars, and pseudogerontoxon.

(i) Vernal ulcerative keratitis is seen with the palpebral form of the disease and is characterised by transversely oval corneal ulcers (Shield-Shaped) confined to the superior half of the cornea. Recently, inferior corneal ulcers associated with palpebral vernal conjunctivitis have been described (Shuler et al., 1988). These have responded well to steroid therapy, giving an impression that they are of hypersensitivity origin.

(ii) Keratoconus (Conical cornea) is another complication that may be associated with vernal conjunctivitis. In this condition, the cornea thins out and bulges as a conical-shaped structure. It has been shown that eye rubbing (as a result of itching) was a dominant factor in two thirds of the patients with keratoconus (Kaseras and Reuben, 1976).

B) **Pathogenesis and Pathology:**

Clinical evidence suggests, that vernal keratoconjunctivitis is a type I hypersensitivity reaction, according to the Coombs and Gell (1975) classification. There is however a possibility that other factors may also play a part in the disease process. In a type I hypersensitivity reaction, an antigen reacts with an antibody (usually IgE) bound to mast cells or circulating basophils, through a special region of the antibody piece. This reaction causes degranulation of the mast cells, and release of mediators of inflammation, mainly histamines, the kinins, prostaglandins and eosinophil chemotactic factor. These released substances cause the clinical picture of the disease (Roit, 1974; J. Vivian Wells, 1982).

Various substances taking part in type I reaction have been isolated in significant amounts in patients with vernal conjunctivitis by using various techniques.

Histamine, one of the most important vasoactive amines released in type I reaction has been found to be significantly raised in the tears of individuals with vernal catarrh. In a study done by Abelson (1977), tear samples from 13 normal individuals and 9 patients with vernal conjunctivitis were

assayed for histamine. Normal subjects had a mean level of 10.3 ng/ml while those with vernal conjunctivitis had a mean level of 38.2 ng/ml.
It was concluded from this study that histamine plays a role in the pathogenesis of vernal conjunctivitis.

IgE is the only immunoglobulin capable of mediating a type I reaction in man. The isolation of significantly high levels of this substance in patients with vernal conjunctivitis from their tears (Brauninger and Centifanto, 1971) and their serum (Allansmith, 1976) strongly supports the idea that vernal conjunctivitis is a type I hypersensitivity reaction. In another observation, patients with hyper-immunoglobulin E were examined for signs and symptoms of vernal keratoconjunctivitis, and 30% were found to have ocular findings similar to those of the disease (Brutus, Abelson and Leving, 1984). Prostaglandins, other mediators of inflammation have also been isolated in significantly raised amounts in tears of patients with this condition (Dhir, Sharma and Garg, 1979).

Clinical experience with sodium cromoglycate, an agent that inhibits the release of mast-cell basophil mediators indicates that mast cell basophil mechanisms are important in vernal conjunctivitis. Various trial therapies have shown various levels of success in alleviating signs and symptoms in vernal catarrh. Easty, Rice and Jones (1972) conducted a double blind placebo controlled study involving 22 patients, in which topical sodium cromoglycate was applied to one eye, and placebo drops to the other eye in the treatment of vernal conjunctivitis for six weeks.

A greater improvement in the condition of one eye as compared to the other was recorded in 18 out of the 22 patients while in the remaining 4, there was no marked therapeutic improvement.
It was concluded from this study that sodium cromoglycate does have a therapeutic response in vernal catarrh in most patients.

Another study in the use of sodium cromoglycate eye drops in vernal catarrh was done by Baryshak and Zarano (1982), in which 19 patients were studied in a placebo-controlled study using 2% sodium cromoglycate eye drops.
There was marked improvement in 16 patients while in 3 patients, there was no response. The 3 patients had no history of atopy and IgE levels were normal.
The conclusion here was that sodium cromoglycate was safe and therapeutically effective in most patients except those who are not atopic.

In a clinical study of vernal keratoconjunctivitis in black children in Southern Africa, 40 children were subjected to different forms of therapy which included placebo, topical steroid (dexamethasone drops) and sodium cromoglycate (Dahan and Appel, 1983). Placebo had no effect in the course of the disease, while topical steroids and sodium cromoglycate were almost equally effective (65%, and 90%, respectively). The follow up period was 2 to 8 weeks.
From this study, the authors recommended a combination of topical steroids and sodium cromoglycate in the treatment of severe cases or acute exacerbation of vernal disease and then to rely on sodium cromoglycate for long term suppression of symptoms if necessary.

Recently, a randomised, double-masked, placebo-controlled multicentre study was conducted for 6 weeks (in the USA) in 12 centres to evaluate the efficacy and safety of cromolyn sodium 4% ophthalmic solution in the treatment of active bacterial vernal conjunctivitis (Foster et al., 1988). Sixty five (65) patients completed the study (35 cromolyn sodium, 30 placebo) and the results showed that cromolyn sodium was significantly more effective than placebo in treating the signs and symptoms of vernal conjunctivitis. As a conclusion, the authors recommended cromolyn sodium as an effective and safe medication in the treatment of vernal conjunctivitis.

In all studies mentioned above, very few side effects were found, usually a burning and stinging sensation. Lastly, the close association of the disease with other known type I hypersensitivity conditions such as hay fever, atopic eczema and asthma, strongly suggests that vernal keratoconjunctivitis belongs to this class of anaphylactic reactions (Allansmith, 1982).

Recent evidence has shown that the eosinophil plays a major role in the pathogenesis of vernal keratoconjunctivitis. The eosinophil in vernal conjunctivitis is granulated, and within the granules is a substance which is highly cationic, known as eosinophil granule major basic protein (Udell, Allansmith, 1981). This compound has been shown to cause massive degranulation of both mast cells and basophils and the subsequent release of histamines. The level of eosinophil major basic protein in the conjunctiva has been closely associated with the severity of the disease, and this substance has also been implicated in the

formation of vernal shield ulcers, giant papillary conjunctivitis and possibly vascular damage. (Trocme, Allansmith, 1989).

There are some factors which indicate that vernal keratoconjunctivitis might not be entirely a type I reaction.

(1) The fact that not all cases respond to di-sodium cromoglycate therapy.

(2) Even histamines and prostaglandin levels do not return to normal after successful treatment with the drug (Sharma and Gupta, 1985).

(3) The histologic picture of the resulting papillary conjunctivitis with extensive infiltration of the lymphocytes plasma cells, basophils also shows that there is more than a hypersensitivity type I condition. In fact this reaction has a similarity with cutaneous basophilic hypersensitivity (a type IV reaction) - (Allansmith, 1977).

Recent conclusions have been that vernal conjunctivitis patients can be divided into two groups, the atopic ones who respond to cromoglycate therapy, and the non-atopic who do not respond to the therapy (Forster et al., 1988).

So, while there is little doubt that a type I hypersensitivity reaction plays a major role in vernal keratoconjunctivitis, it is possible that other immunologic mechanisms play a part together with genetic, and environmental factors. This is still under intense study.

Pathology:

According to Duke-Elder (1965) the essential pathological changes are:

Epithelial proliferation:

This is more evident in the limbal region where there is massive epithelial overgrowth into a layer 30-40 cells deep.

Fibrous tissue proliferation:

Followed by hyaline degeneration, this is less evident in the limbal form.

Substantia propria with massive infiltration by eosinophils, lymphocytes plasma cells, and neutrophils. Takakusaki (1969) made an intensive electron microscopy study of the palpebral conjunctiva and his findings supported the above conditions. He noted secretory activity of ordinary epithelial cells, and mast cells with granules of various sizes, together with globule containing (Russel bodies) mast cells.

Morgan (1971) describes massive proliferation with concomitant degeneration of the epithelium with increase in number of the goblet cells. The epithelium is transformed into stratified columnar cells sometimes keratinised. Trantas spots have also been described histologically, these are circumscribed ares of epithelial cells undergoing rapid degeneration and forming an amorphous mass containing degenerated eosinophils.

The papillae in vernal conjunctivitis have the histological features of stratified squamous epithelium with reduced goblet

cell population infiltrated with eosinophils, basophils, polymorphonuclear cells and occasionally lymphocytes. The stroma has large numbers of lymphocytes, plasma cells, occasionally polymorphonuclear cells and macrophages. The number of mast cells is increased.

The mast cells in vernal keratoconjunctivitis, are typically degranulated; whereas the oesinophils are granulated (Kimura, Thygeson, 1955; Allansmith, Greiner, 1978) and these granules have been found to contain eosinophil granule major basic protein, a cationic substance responsible for some of the reactions in the disease process (Trocme and Allansmith, 1989).

C) **TREATMENT:**

There no single effective and accepted method used in the treatment of vernal keratoconjunctivitis. Various therapeutic measures have been attempted in the treatment of the disease with limited success in some and with no therapeutic effects in others.

Therapy is usually aimed at reduction or abolition of symptoms and the reversal (total or partial) of structural changes affecting the eye e.g. papillae. Both surgical and medical approaches to the treatment of the disease have been used, either singly or in combination.

I) **MEDICAL THERAPY:**

(a) Steroids:

These are strong anti inflammatory drugs. Their wide range of anti-inflammatory activity has been summarised (with reference

to the eye) by Duke Elder and Ashton (1951) as follows:

- Reduction of the permeability of the normal capillaries.
- Exudation (associated with inflammation) is inhibited.
- Inhibition of cellular infiltration and formation of granular tissue.
- Reduction of fibroblastic activity and consequent retardation of healing wounds.
- Reduction of inflammatory reaction to the eye.

Indeed, steroids have been and are still being used in a wide range of inflammatory conditions. In vernal catarrh, their efficacy both as local instillation and systemic medication has been proved by Neumann (1958) in a series of 400 patients. Other authors thereafter, found corticosteroid useful albeit for a short term therapy, used topically (Easty, Rice and Jones, 1971; Allansmith, 1982). Todate, they are still being used widely. However, it has been found that the long term use of corticosteroids both topical and systemic carries considerable risks of complications; which may threaten vision.

David et al. (1969) has summarised the effects of steroids to the eye as; steroid induce glaucoma to susceptible individuals, cataracts, and an increased susceptibility to infections especially fungal and/or viral (especially herpetic). The drug despite its high potency against inflammation, is not ideal for a chronic disease like vernal conjunctivitis. There is need for safer alternatives to corticosteroids. Short term therapy, topically, is still recommended as in refractory cases of vernal conjunctivitis, in combination with cromolyn sodium (Forster et al., 1988).

(b) Aspirin:

This is a drug that has been tried in the treatment of vernal conjunctivitis in three patient with refractory vernal conjunctivitis with encouraging results(Abelson, Brutus and Weston, 1983). It is known that aspirin is a prostaglandin synthetase inhibitor (Vane, 1971) and its effect has been well demonstrated in human plateletes (Smith and Willis, 1971) and dog spleen (Ferreira, Moncada and Vane, 1971). It is now established that PGE-type prostaglandins are released in a variety of experimental and clinical allergic conditions, prostaglandins being one of the mediators of inflammation. High levels of prostaglandins F were found significantly increased in tear films of patients with acute vernal conjunctivitis (Dhir, Garg and Sharma, 1979) while in another study, high levels of prostaglandin E_2 were found in patients suffering from vernal conjunctivitis. It is with these facts in mind that Abelson, Brutus and Weston (1983) conducted a study on the clinical effects of aspirin in 3 patients suffering from intractable vernal conjunctivitis. This turned out to be a success, and they recommended it as a supplementary drug in treating vernal conjunctivitis. A study emulating the above in five (5) refractory cases of vernal conjunctivitis however, proved to be disappointing (Ben Ezra, Pe'er and Bradsky 1986).

A study involving a larger number of patients with a control group is needed to substantiate efficacy of this drug which if proved will benefit a lot of patients since it is almost universally available. Side effects of gastric irritation, and tinnitus should be closely looked for.

(c) Sodium cromoglycate, is a mast cell membrane stabiliser, which is now widely used and recommended as the drug of choice in vernal conjunctivitis (Easty, Rice and Jones, 1972; Sharma and Gupta, 1985; Forster et al., 1988) after controlled double blind clinical studies, using eye drops preparations. However, Abelson et al. (1981) found that not all patients respond to the drug. Moreover, histamines and prostaglandins levels do not return to normal after treatment with sodium cromoglycate (Sharma and Gupta, 1985), it may need to be combined with local steroids. The limiting factor in our environment concerning this drug is its unavailability, and when available, its high cost.

Currently, medical therapy in vernal conjunctivitis is focused in the development of membrane stabiliser drugs which are more potent than Cromolyn sodium. Two new drugs still under investigations, necromil sodium (Tilade) which is 100 times more potent than sodium cromoglycate and lodoxamine tromethamine have shown promising results in limited studies in a variety of allergies (Allansmith and Lass, 1990).

(d) The use of **cycloporine** eye-drops for the treatment of severe vernal keratoconjunctivitis has shown promising results. (Ben Ezra et al., 1986). In series involving twelve (12) children with severe chronic vernal keratoconjunctivitis treated with 2% cyclosporine eye-drops, eleven of the 12 children showed clinical improvement after only one week of treatment. Further control studies are needed to evaluate therapeutic effects of the drug.

(e) The use of **ocular decongestants** has been tried in a double blind study, as therapy for allergic conjunctivitis. It has been shown that the drugs have no ability to remove the symptoms (Lanier, Tremblay and Smith, 1983).

II) **SURGICAL TREATMENT:**

Several surgical methods have been used in the treatment of vernal conjunctivitis. Success in eliminating the signs and symptoms have been reported in cryotherapy and papillae excision with mucous membrane grafting.

(a) Cryotherapy: Application of low temperatures to the eye for therapeutic purposes was first described by Bishop Harman in 1910 in which he successfully treated cases of trachoma (Bietti, 1968). The first described cases treated with cryosurgery in vernal conjunctivitis are reported by P. Veie and Lotert-Jacob in 1928.

After that there was a lull in the use of cryotherapy until 1967 when, after clinical success, Cassanova recommended the use of cryosurgery in vernal keratoconjunctivitis. It has been shown that low temperature are destructive to ocular tissues (Amoils, 1975). The rationale for cryotherapy is destruction of histamine producing tissues (papillae) and thus bring about both symptomatic relief and structural changes to the affected parts whether palpebral or limbal.

In an uncontrolled study by Mtanda and Sangawe (1983), 34 patients were subjected to cryotherapy, and followed up for 5 months. There was marked improvement in signs and symptoms in 94% of patients with visual improvement in 50% of the 6 cases with impaired vision. It was recommended from this study that cryosurgery be the method of choice in the treatment of vernal catarrh.

(b) Cryotherapy and desensitisation: An earlier study by Amoils (1975) had also shown marked symptomatic relief in 10 out of the

12 patients who had undergone cryosurgery; and 100% success when cryosurgery was combined with desensitisation.

(c) Excision of papillae:

In yet another series, five patients with severe palpebral conjunctivitis had dramatic symptomatic relief after total excision of the cobblestone papillae from the tarsal conjunctiva, and replacement with a mucous membrane graft (Tse, Baevelat and Mandelbaum, 1983). This method is still debatable and has not found wide acceptance for fear of long term sequelae like circatrisation and tear film abnormalities. However, these sequelae have not been observed so far.

(d) Tarsectomy with advancement of levator muscle fibres had earlier been recommended (Sugar, 1962) but has now lost acceptance due to non-abolition of most symptoms and resultant structural deformities such as ptosis.

(e) Superficial keratectomy

Buckley (1981) treated patients with vernal plaque medically and surgically. Of the fourteen patients treated medically only three (<1/4) responded well to therapy after one week of therapy compared to 18 (50%) who responded well to surgical therapy-superficial keratectomy. Superficial keratectomy is therefore recommended in vernal plaque compared to medical (steroid) therapy.

From the reviewed literature above it seems that both surgical and medical methods of treatment used in vernal conjunctivitis have limited efficacy as experienced by various authors and with these variations in effectiveness it is justified therefore, to make an attempt to compare the actual

effects of the various treatment modalities available in our set up by a single-blind placebo controlled study, with the aim of finding the best therapeutic alternatives in our environment.

SPECIFIC OBJECTIVES

Major objective:

To carry out a single blind re-evaluation of the various forms of treatment currently available for the treatment of Vernal Keratoconjunctivitis in order to discover the most efficacious mode of treatment.

Minor objectives:

1. To find the age and sex distribution of vernal conjunctivitis in our population.
2. To find the clinical presentation of vernal conjunctivitis in our environment.
3. To find out the prevalence of other atopic states (asthma, rhinitis and eczema) in those patients with vernal conjunctivitis and in their family members.
4. To find The proportion of patients with significant visual impairment from vernal conjunctivitis.
5. To identify the predominant form of the disease i.e whether limbal, palpebral or mixed type.

MATERIALS AND METHODS

Patients Selection:

Patients were selected from the general out-patient eye clinic. Those found to have active vernal conjunctivitis were referred to a special clinic for further evaluation. Patients were included in the study if:

(i) They had no therapy at all since the onset of the condition ie newly diagnosed.

(ii) They had been without therapy for the previous six months and presented with signs and symptoms of the disease.

An informed consent was obtained from the patient or parent/guardian of the affected children. Other criteria for inclusion into the study were: either sex and any race, able to follow instructions, and those who were willing and able to make the required study visits.

Patients with (i) bacterial infections or (ii) those wearing contact lenses and/or taking systemic drugs which might interfere with the results of the study (eg. steroids) were excluded from the study.

Clinical Evaluation:

An initial visit identification data was taken after which a thorough history was taken pertaining to symptoms of itching, tearing, sandy sensation, photophobia and discharge and their degree of severity, which were scored on a basis of 0 to 3 or 4 for each symptom for the worst eye. (See annex I).

Patients or their parents were also questioned about the age of onset of the condition, the seasonal variations of the condition, a personal history of other allergic conditions eg. asthma, eczema and rhinitis and a family history of vernal keratoconjunctivitis, allergic rhinitis, atopic eczema and asthma.

A full examination was then carried out including taking a corrected visual acuity (distant) which was done by using a standard Snellen's chart; Schiotz tonometry was done initially in all patients who were old enough to be cooperative, and in follow up visits readings were taken in those falling in the above category in the topical steroid group only. Then, an external ocular examination was performed by direct illumination using a torch with special attention to the lids (inner and outer part), the conjunctiva, and the cornea for any corneal manifestations. A detailed examination of the outer eye was then done using a Haag-Streit slit lamp. The presenting signs were scored on the basis of severity 0-3 or 0-4 for the worst eye. The evaluated signs included conjunctival hyperaemia, papillary hypertrophy, limbal congestion or oedema, Trantas' dots and corneal signs (eg. punctuate lesions). (See annex II).

The severity of signs and symptoms and their appropriate scores are as shown in the following tables:-

SYMPTOMS SCORE

SYMPTOM	SEVERITY	SCORE
ITCHING	None	0
	Mild (intermittent)	1
	Moderate (continuous awareness without desire to rub)	2
	Severe (continuously aware with desire to rub)	3
	Incapacitating, Insists: - on rubbing - cannot carry out daily activities	4
TEARING	None	0
	Mild (watery feeling)	1
	Moderate (tears pod in conjunctival sac	2
	Severe (tears roll down the cheeks)	3
SANDY SENSATION	None	0
	Mild (occasional distant feeling)	1
	Moderate (patient continuously aware but not incapacitating)	2
	Severe (intolerable sandy feeling)	3
PHOTOPHOBIA	None	0
	Mild	1
	Moderate	2
	Severe (incapacitating, inability to open eyes.	3
DISCHARGE	None	0
	Mild (occasional)	1
	Moderate	2
	Severe (discharge continuous, vision blurred)	3

SCORE CHART FOR SIGNS

SIGN	SEVERITY	SCORE
CONJUNCTIVAL HYPERAEMIA	None	0
	Involving bulbar or palpebral only	1
	Involves both bulbar and palpebral	2
	Profuse involvement of both the bulbar and palpebral conjunctiva	3
PALPEBRAL PAPILLAE	None	0
	Uniform mild papillary reaction	1
	Some giant papillae seen.	2
	Cobblestone papillae	3
LIMBAL PAPILLARY HYPERTROPHY	None	0
	Discrete reaction 1 quadrant	1
	Discrete reaction 2 quadrants	2
	Discrete reaction 3 quadrants	3
	All quadrants involved	4
TRANTAS SPOTS	None	0
	Involving 1 quadrant only	1
	Involving 2 quadrants only	2
	Involving 3 quadrants	3
	All quadrants	4
CORNEAL LESIONS	None	0
	1 quadrant involvement	1
	2 quadrants involvement	2
	3 quadrants involvement	3
	All quadrants involved or control lesions	4

The cornea was topographically divided into 4 quadrants with the vertical meridian passing through 12- and 6-O'clock, and the horizontal meridian passing through 3- and 9-O'clock.

Fluorescent staining was done on all patients to rule out any corneal involvement. All patients were examined with a keratoscope (Placidos disc) to detect any associated keratocmus. Direct ophthalmoscopy was done in each patient to rule out any retinal or optic disc causes of lowered visual acuity.

During the follow up visits, a brief history concerning the severity of the symptoms was elicited, which was followed by a thorough examination of the outer and inner eye as per first visit.

Selection into therapy: Patients were randomly assigned to one of the 4 group therapies. After initial clinical assessment by the author, a senior ophthalmic nurse randomly assigned the patients into one of the 4 therapy groups. The nurse also dispensed the medication and gave instructions on their use. In this way the author did not know which patient received which therapy i.e. single blind study. Clinical assessment in the follow up periods was done by the author. Cryosurgery was also done by another doctor.

The 4 groups were:

1. Topical steroids
2. Cryotherapy
3. Oral aspirin
4. Placebo

Modes of treatment:

A. **Topical steroids:**

Patients in this group were given a steroid-antibiotic

solution for use, and instructed to instill into both eyes, two drops four times daily, during the study period. They were told to report to the clinic anytime in case the condition worsens, with pain, photophobia or visual impairment assessment was done 1 week after initiating therapy, then 2 weekly thereafter. The intended period for follow up was six weeks.

B. **Cryotherapy:**

This was done using the Amoils Cryo unit, which uses carbon dioxide gas for freezing, with a cataract probe. The cataract probe, with a temperature of -70°C was applied "side on" over the site of the papillae, over the averted upper lid or limbus, depending on whether it was a limbal type, or palpebral type. Each application lasted for about 40 seconds; but shorter freezing times were used at the limbus, (20 sec) to minimize possible corneal endothelial damage. Both eyes were treated at the same sitting under local anaesthesia (2% retrobulbar injection-lignocaine) for adults, and general anaesthesia for children.

After cryosurgery, an antibiotic steroid solution was immediately applied to both eyes and binocular pads were applied. The pads were removed after 48 hours and usually by this time, the post-operative oedema had subsided considerably.

A steroid-antibiotic solution (adremycin eye drops - organon, consisting of chlorprednisolone acetate 0.1% and neomycin sulphate 0.5%) was applied topically for four

days only-twice daily ie. every twelve hours. Follow-up of this group was done at intervals as in group A. No other drug were prescribed during the follow-up period.

C. **Oral aspirin:**

These patients were provided with aspirin tablets with instructions to use 300 mg three times daily for adults, and 150 mg for 10-16 years of age and 5 mg per kg body weight for those under 10 years - all taken after meals. Patients were instructed to be particularly alert for symptoms of tinnitus, epigastric pain, or abnormal bleeding, and report immediately in case they develop. This was a contraindication to continuation of therapy. Follow up was done as in the 2 previous groups.

D. **Placebo:**

Methylcellulose 0.5% eye drop were provided to the patients and they were instructed to apply two drops in each eye three times daily. A worsening of the situation was considered a contraindication to therapy and the patient was thus referred back to the general clinic for continuation of medication.

A worsening of the condition was regarded as incapacitating itching, visual impairment and photophobia. The presence of corneal ulcers or punctate keratitis was an indication for discontinuation of therapy.

STATISTICAL ANALYSIS:

Data from patient who withdraw from the study after 2 weeks of therapy were taken into account, while that of those who withdraw before 2 weeks were discarded.

The average scores for signs and symptoms for each group were assessed and the differences between the baseline and endpoint were calculated as a ratio with respect to placebo scores. This would give the effectivity of a given drug compared to placebo (odd-ratio method). A comparison of different drug effectivities could thus be made.

Definition of terminologies:

1) Family: Is used to mean father, mother and siblings.
2) Significant visual loss

A visual acuity of 6/18 or less in the better eye.

R E S U L T S

A total number of 61 patients were examined initially between February and November of 1989. Of these, 36 (59.1%) were males while 25 (40.9%) were females. Mean follow-up period was four (4) weeks. Mean age of patients who underwent initial examination was 10.7 years. The minimum age was thirteen(13) months while the oldest patient examined was 27 years.

The age group with the largest proportion of patients was 0 - 5 which had 18 (29.5%) while the smallest proportion of patients was in the > 20 years group with 7 (11.5%) patients.
There was no statistical significance of male preponderance (P > 0.990).

TABLE I: DISTRIBUTION OF PATIENTS BY AGE AND SEX

AGE GROUP (YRS)	MALE	FEMALE	TOTAL	PERCENTAGE
0 - 5	12	6	18	29.5
6 - 10	8	7	15	24.6
11 - 15	7	6	13	21.3
16 - 20	5	3	8	13.1
> 20	4	3	7	11.5
TOTAL	36	25	61	100.0

P > 0.990

TABLE II: DISTRIBUTION OF DISEASE TYPES BY AGE GROUPS

AGE GROUP (YRS)	PALPEBRAL	LIMBAL	MIXED	TOTAL
0 - 5	--	6	12	18
6 - 10	6	3	6	15
11 - 15	3	--	10	13
16 - 20	2	--	6	8
> 20	--	--	7	7
TOTAL	11 (18.0%)	9 (14.8%)	41 (67.2%)	61

P > 0.95

Of the patients examined 11 (18.0%) had the palpebral type of vernal conjunctivitis while 9 (14.8%) had limbal type of the disease. Forty one (41) patients (67.2%) had mixed type. The limbal type of the disease was confined to the 0 - 10 years age group while the mixed type was found well distributed in all age groups. Most of the patients had the mixed type of the disease.

The limbal type consisted of conjunctival gelatinous swelling with circumcorneal opacification of about 2 mm from the limbus with a micropanus. There was also typical pigmentary invasion of the cornea. Three patients with mixed type of the disease had cobblestone papillae while the rest had fine palpebral papillae well distributed in the upper eyelid. Mixed type of disease had no statistical significance over others; ($P > 0.95$).

TABLE III: PROPORTION OF ASSOCIATED TYPE I CONDITIONS IN THE FAMILY AND IN PATIENTS WITH VERNAL CONJUNCTIVITIS

	ASTHMA	ALLERGIC RHINITIS	ATOPIC ECZEMA	VERNAL CONJUNCTIVITIS
FAMILIAL HISTORY	15 (24.6%)	----	---	13 (21.3%)
ASSOCIATED IN THE PATIENT	11 (18.0%)	7 (11.5%)	4 (6.5%)	----

Table III shows the proportion of associated type I hypersensitivity reactions in the family and in patients with vernal conjunctivitis. Asthma was the commonest associated condition both in the family where 15 patients (24.6%) had a positive family history. Eleven (11) patients (18.0%) had asthma associated with vernal conjunctivitis. Thirteen (13) patients (21.3%) had a positive family history of vernal conjunctivitis, while 7 (11.5%)

of the patients had associated allergic rhinitis which was confirmed by the ENT surgeons.

Atopic eczema was found in only 4 (6.4%) of the patients. There was no patient with a family history of atopic eczema or allergic rhinitis.

TABLE IV : VISUAL ACUITY IN PATIENTS WITH VERNAL CATARRH

	VISUAL ACUITY	No. OF PATIENTS AND PERCENTAGE
NORMAL	> 6/18	39 (78.0%)
LOW VISION	6/60 - 6/18	11 (22.0%)
	3/60 - 6/60	-------
BLINDNESS	1/60 - 3/60	-----
	LP - < 1/60	-----
	NLP	------
TOTAL		50 (100%)

Fifty (50) patients were old enough and willing to have their visual acuity taken by the Standard Snellens' Chart. Thirty nine (39 or 78.0%) of the patients had normal visual acuity while 11 (22%) low vision. The cause of low vision was usually corneal manifestations of the disease (punctuate keratitis, superficial scars). There were no vernal corneal ulcers found in all the patients, and no patient had keratoconus. The lowest vision found in the patients examined was 6/36. Distribution of **"low-vision"** patients in group therapies was:

steroid	2		placebo 3
cryo	4	and	ASA 2

PRESENTING SYMPTOMS

Table V shows the frequency of presenting symptoms in the patients examined. All patients presented with itching as the main symptom, while 46 patients (75.4%) presented with tearing. Visual impairment was a complaint in 13 (21.3%) patients. Photophobia was the least prevalent symptom being present in only 11 (18.0%) of the patients.

TABLE V

SYMPTOMS	NO OF POINTS AND PERCENTAGE
ITCHING	61 (100%)
TEARING	46 (75.4%)
SANDY SENSATION	33 (54.1%)
PHOTOPHOBIA	11 (18.0%)
DISCHARGE	26 (42.6%)
VISUAL IMPAIRMENT	13 (21.3%)

There were no seasonal variations in the severity of the symptoms in all patients. Itching was more severe and persistent in the younger age group (5 - 10 years) than in the older patients (> 10 years).

THERAPY GROUPS

The therapy groups which were randomly selected had the following characteristics: Summarized in table VI.

(1) **STEROID GROUP** had a total of 16 patients with 11 males (68.75%) and 5 females (31.25%). The mean age was 9.75 years.

(2) **PLACEBO GROUP:** This group had a total of 15 patients with 6 males (40%) and 9 females (60%). The mean age was 11.0 years.

(3) **CRYO GROUP:** This group also had a total of 15 patients in which 11 were males (73.3%) while only 4 (26.7%) were females. The mean age group was 13.7 years. This was the highest mean age compared with all other groups .

(4) **ASPIRIN GROUP:** There were 15 patients in this group with 8 males (53.3%) and 7 females (46.6%). The mean age was 9.3 years.

TABLE VI: DISTRIBUTION OF PATIENTS IN GROUP THERAPIES

THERAPY GROUP	MALE	FEMALE	TOTAL	MEAN AGE (YEARS)
STEROID	11 (68.75%)	5 (31.25%)	16	9.75
PLACEBO	6 (40.0%)	9 (60.0%)	15	11.0
CRYO	11 (73.3%)	4 (26.7%)	15	13.7
ASA	8 (53.3%)	7 (46.6%)	15	9.3
TOTAL	36	25	61	

TABLE VII: RESULTS OF THERAPIES IN DIFFERENT GROUPS

INITIAL EXAMINATION				FINAL EXAMINATION			
THERAPY GROUP	NO. OF PATIENTS	TOTAL SCORE	MEAN SCORE	NO. OF PATIENTS	TOTAL SCORE	MEAN SCORE	ODD RATIO
STEROID	16	216	13.5	12	108	9.0	1.450
PLACEBO	15	143	9.5	11	101	9.2	1.000
CRYO	15	144	9.6	10	62	6.2	1.499
ASA	15	176	11.7	13	135	10.4	1.089

THERAPEUTIC RESULTS

(A) **Steroid group:**

There was a significant reduction in severity of the disease as shown by the severity score. Twelve (12) patients met the criteria for follow-up. Patients in this group had considerable improvement in the symptoms, and signs eg Trantas spots, and punctate keratitis. Palpebral papillae structurally remained unchanged in most patients though limbal conjunctival hyperaemia improved considerably. There was no glaucoma, cataract or corneal ulceration noted as a result of the therapy. The odd ratio with respect to placebo was 1.45.

(B) **Placebo Group:**

There were 11 patients assessed in the final clinical evaluation. Initially most reported improvement in the symptoms, but this did not last long and the clinical picture returned to pre-treatment severity. There were no structural changes in this group. Two (2) patients had vision threatening keratitis and were discontinued from the therapy group.

(C) **Cryotherapy:**

Ten (10) patients of the 15 initially examined and treated were followed up enough to be included in the final analysis. Initially there was mild improvement in the objective assessment eg. conjunctival hyperaemia while the symptoms improved within a few days after initiation of the therapy.

There was progressive improvement in the signs (palpebral and limbal papillae, conjunctival hyperaemia) with time, while the symptoms, eg. itching were also reduced. The odd ratio with respect to placebo was 1.499.

(D) **Aspirin Therapy:**

Of the 15 patients initially examined, 13 were followed up enough to be included in the final assessment. There was no significant change in the final mean score of disease severity. One patient was discontinued from the group therapy due to a mild abdominal complaint, the other absconded. The odd ratio with respect to placebo was 1.089.

DISCUSSION

Age and Sex

Vernal conjunctivitis is a disease of children and young adults, and in this study it has been shown that the age ranged from 13 months to 27 years, with a mean of 10.7 years. In a similar study, Mtanda and Sangane (1983) found the range to be 4 - 36 years, with a mean of 13 years; while Dahan and Appel (1983) found the range of 2½ to 18 years with a mean of 7½ years. Duke Elder (1965) reports the range of the disease in the young to be 6 - 20 years and the above mean ages fall within this range, including that found in this study.

In this study, the male to female ratio of 1.4:1 closely agrees with that of Mtanda and Sangawe (1983) of 1.2:1; however, it disagrees with the high ratio of 4:1 found in other series by Forster et al. (1988). The former study groups were smaller than the latter. All in all, the results show that the disease is more predominant in males than in females with different ratios in different places; the reason of which still remains unknown but may be attributed to ultra-violet exposure (i.e males are more exposed due to outdoor activities) or genetic factors.

Distribution of Disease Types

This study has shown that the predominantly limbal form (14.8) was the least common type of the disease while the mixed type (67.2%) was the most common.

This finding differs from other findings in black patients (Sandford Smith, 1981; Dahan and Appel, 1983) where it was found that the limbal form of the disease was predominant, raising the question whether there was a hereditary aspect to the disease.

In agreement with the previous study by Sandford Smith (1981) in black patients is the fact that the bulbar disease (limbal form) was found only in the younger age group (mean 2.6 years) while the palpebral disease was found in the older group (mean 16.7 years), there was a slightly different form of classification. There is a possibility that the disease mainly starts as a limbal form, then passes through the mixed form transition before it ends up as the palpebral type in older patients. These results however, agree with previous observation (Duke-Elder, 1965) which places the mixed form of the disease as the most common type.

The limbal findings are in agreement with previous authors of limbal papillary hypertrophy, limbal conjunctival oedema, circumcorneal opacification and a micropannus which was mainly on the upper 1/2 but sometimes extended to 360°. Typical cobblestone papillae were a rare finding (4.9%). This has been the case in Africans (Sandford Smith, 1979; Dahan, 1983) pointing out again to the possibility of a genetic component. Dahan (1983) found cobblestone papillae in Asians only.

ASSOCIATION WITH OTHER TYPE I HYPERSENSITIVITY REACTIONS

While the aetiology of vernal conjunctivitis is still largely conjectural, the fact that it has been associated with other allergic conditions points to the possibility that it could be largely attributed to allergic reactions of the type I variety.

Frankland (1971) found a positive family history of vernal keratoconjunctivitis in 25% and a 5% association of hay fever rhinitis in the population of 80 patients. There was no reported

association with asthma in this study, which resembles with those of Sandford Smith (1979) in which no association of asthma was found and also a low incidence of associated atopic conditions.

In this study there was a family history of asthma in 24.5% of the patients and also a family history of vernal diseases in 21.3% of the patients. There was no family history of eczema or rhinitis.

Patients with associated allergic conditions were asthma (18.0%), allergic rhinitis (11.5%) and atopic eczema (60%). The relatively high incidence of associated atopic diseases can be compared with those found in a multicentre study done in the USA (Foster et al., 1988) in which a number of patients had associated conditions of asthma (30.8%), rhinitis (30.8%) and eczema (36.1%). (The percentages are my calculations based on the figures given in the study). The hypothesis that urban patients have more atopic diseases than rural patients (Sandford-Smith, 1979) could apply here as this study involved mainly urban patients; it could be compared to the USA study which mainly involved urban communities as well.

In view of the new developments in membrane stabiliser drugs in vernal catarrh, it could be meaningful to conduct an objective study to determine the proportion of atopic individuals in our set up. This would give an indication as to what extent the response would be to drugs like sodium cromoglycate which have proved to be more effective in atopic individuals.

VISUAL ACUITY

Contrary to a previous observation by Sandford Smith (1979) that the danger of visual impairment is low in vernal catarrh, this study has shown that there is a considerable proportion of patients (22%) who had cow vision all due to corneal involvement especially superficial punctal keratitis, superficial scars and limbal opecifications extending to the central area. These findings can be compared with those by Mtanda and Sangawe (1983) who found six (6) patients out of 34 with visual impairment due to vernal conjunctivitis.

Dahan et al. (1983) described visual threatening limbal lesions encroaching on the cornea. Fortunately these corneal lesions respond to therapy and the visual impairment is usually reversible in a great proportion of patients as shown in the previous two studies.

Corneal ulcers are rare in vernal conjunctivitis and the absence of corneal ulcers in this series could be compared to that by Dahan (1983) and Foreter (1988), while a few cases were found by Sandford Smith (1979).

As in other reports there has been no reported case of blindness from purely vernal conjunctivitis. The absence of keratoconus in this series possibly explains the low incidence of the condition not only in association with the disease, but also in the general population.

PRESENTING SYMPTOMS:

The main presenting symptoms were itching (100%) and tearing (75%) and these are the ones that usually prompt the patient to seek medical advice.

The proportion of visual impairment found clinically almost corresponds to that of patients complaining of visual impairment. The absence of seasonal variation noted may be described by the usually hot, humid weather experienced throughout the year in this area; although this slightly differs with what has been experienced by other studies in similar weather conditions (Sandford- Smith, 1979). The absence of seasonal variations has also been mentioned by Mtanda and Sangawe (1983) who conducted a similar study in our centre.

THERAPY GROUPS AND THERAPEUTIC RESPONSES

Steroid Group:

Topical steroids have been known for a long time as effective drugs for the relief of symptoms in vernal conjunctivitis (Neumann, 1958; Dahan, 1983). In this study steroids have been shown to have a higher efficiency in controlling symptoms and signs of vernal conjunctivitis than oral aspirin or placebo. This study has shown steroids to be less effective than cryotherapy.

The high success rate reported in cryotherapy (Amoils, 1975) compared to that reported in steroids favour the above results although a longer follow up study needs to be done using a larger study population. This however, needs to be done with caution due to the known effects on glaucoma and infections in prolonged use of steroids.

Cryotherapy

Cryotherapy has been shown to be the most efficacious means of controlling the signs and symptoms of vernal conjunctivitis, being about 1.5 stronger than placebo.

Previous studies have supported this finding. Patient review has found that the change involve not only in the relief of most symptoms but also in most signs eg papillae, and conjunctival hyperaemia.

The disadvantages of cryotherapy are that it must be performed in hospital under either general or local anaesthesia, and sometimes has to be repeated several times to get the relief (Mtanda, Sangawe, 1983). However, in a society where the supply of medicines is intermittent and expensive, cryotherapy (as shown by this study) may prove to be the method of choice in intractable disease. The high drop-out in this group therapy can be explained in two ways: first that the patients might have been discouraged by not having any drugs being dispensed to them in the follow up period; and secondly it is likely that with the cessation of symptoms patients did not find it necessary to go on attending to hospital taking into account the transport problems, and the long waiting time at the clinic due to the overcrowding.

Aspirin group:

Aspirin has not prove to be as effective in vernal catarrh as the other two active drugs. Contrary to the results of the initial study by Abelson (1983) where this was used as adjunct therapy these results together with those of Sharma and Gupta (1985) disagree with the above findings. As the function of aspirin is

closely related to the prostaglandin synthesis, there is a need to evaluate the role of prostaglandins in our patients; as these may be minimal in our patients. Aspirin remain as a drug to be used as adjunct therapy and not alone in the management of vernal conjunctivitis.

Placebo

While the placebo might be having soothing effects, on the whole, it did not prove efficient in the control of signs and symptoms of the disease. This was expected, although recent literature has shown that 70% of patients who used placebo in experiments have a 'drug effect' and therefore this calls for new methods to be used to evaluate anti-allergic drugs as suggested by Abelson et al., (1990), by conjunctival allergic challenge.

SUMMARY

Sixty one patients with vernal conjunctivitis were examined and found to have the outstanding features that differ with other previous studies, that is the high proportion of patients with history of atopy, and the predominance of the mixed type of the disease in the African.

The patients were randomly selected into therapy groups and subjected to topical steroids , placebo, cryotherapy and aspirin. In this series, cryotherapy proved to be more efficacious than steroids and aspirin and is therefore recommended as the method of choice in the management of intractable vernal conjunctivitis.

With the discovery of newer and more efficacious topical medications however, cryotherapy may become less preferable due to inconveniences of hospital admission and sometimes being subjected to general anaesthesia.

There is a need to evaluate objectively the degree of atopy of our patients by the assay of eg. histamines, prostaglandins, as this would give not only the possibility of responding to newer drugs but may be used to pharmacologically assess the response to all types of therapy since they have been found in previous studies to go down with improvement in clinical signs and symptoms.

REFERENCES

Abelson M.B., Histamine in Human Tears, Am. Journal of Ophth., **83:** 417, (1977).

Abelson M.B., Brutus S., Weston B.A. and Judith H., Aspirin Therapy in Vernal Conjunctivitis, Am. Journal of Ophth., **95:** 502, (1983).

Abelson M.B., Chambers W.A. and Smith L.M., Conjunctival Allergen Challenge A Clinical Approach to Studying Allergic Conjunctivitis, Arch. of Ophth., **108:** 84, (1990).

Allansmith, M.R., Vernal Conjunctivitis, in Clinical Ophthalmology, Vol. 4, Chap. 9, Harper and Row Publishers, Philadelphia, (1982). Edited by Thomas Doanne.

Allansmith M.R. and Greiner J.V., Number of Inflammatory Cells in the Normal Conjunctiva, Am. Journal of Ophth., **86:** 250, (1978).

Allansmith M.R. and Lass J.H., Mast Cell Function, Problems Described, Ophthalmology Times, March 1990, pg 6.

Allansmith M.R. et al., Tissue, Tear and Serum IgE Concentration in Vernal Conjunctivitis, Am. Journal of Ophth. **81:** 506, (1976).

Allansmith M.R., Korb, D. R., Greiner, J. V., Henriquez, A.S., Simon, M. A. and Finnemore, V. M., Giant Papillary Conjunctivitis in Contact Lens Wearers, Am. Jour. Ophth., **83**, 697, (1977).

Amoils S.P., Cryosurgery in Ophthalmology, Kent. Pitman Medical, (1975).

Baryishak Y.R., Zavaro, A. and Monselise, M., Vernal Keratoconjunctivitis in an Israel Group of Patients and its Treatment with Sodium Cromoglycate, Br. Journal of Ophth.,**66:** 118, (1982).

Ben Ezra D., Pier J., Brodsky M. and Cohen E., Cyclosporin Eyedrops in the Treatment of Severe Vernal Keratoconjunctivitis, Am. Journal of Ophth., **101:** 278, (1987).

Bietti G.B., Development of Cryotherapy, Trans. Ophth. Soc. UK., **vol. LXXXVIII:** 78, (1968).

Brauninger G.E. and Centifanto, Y.M., Immunoglobulin E in Human Tears, Am. J. of Ophth. **71:** 558, (1972).

Brutus S., Abelson M.B. and Leving D, Vernal Conjunctivitis in the Hyperimmunoglulinaemia E Syndrome, Ophthalmology, **91:** 1213, (1984).

Buckley R.J., Vernal Keratopathy and its Management, Trans.Ophth. Soc. UK, **101:** 234, (1981).

Coombs R.R.A. and Gell, P.G.H., Classification of Allergic Reactions Responsible for Clinical Hypersensitivity and Disease, in: Clinical Aspects of Immunology, Blackwell, (1975).

Dahan E. and Appel, R., Vernal Keratoconjunctivitis in the Black Child and its Response to Therapy, Br. Journal of Ophth., **67:** 688, (1983).

David D.S. et al., Ocular Effects of Topic and Systematic Cortico Steroids, The Lancet, **2:** 149, (1969).

Dhir S.P., Sharma Y.R, Garg S.K. and Lath N.K., Prostaglandins in Human Tears, Am. Journal of Ophth., **87:** 403, (1979).

Duke-Elder S., Systems of Ophthalmology, Vol. VIII, Diseases of the Outer Eye Part II, Henry Kimpton, London, (1965).

Duke-Elder S. and Ashton N., Action of Cortisone on Tissue Reaction of Inflammation and Repair, with Special Reference to the Eye, Br. Journal of Ophth., **35:** 695, (1951).

Easty D.L., Rice N.S.C. and Jones B.R., Clinical Trial of Topical Disodium Cromoglycate in Vernal Keratoconjunctivitis, Clinical Allergy, **2:** 99, (1972).

Easty D., Rice N.S.C., Garner A., Jones B.R. and Tripathi R., Vernal Keratoconjunctivitis and its Management, Trans. Ophth. Soc. UK., **91:** 467, (1971).

Ferreira S.H., Moncada S. and Vane J.R., Indomethacin and Aspirin Abolish Prostaglandin Release from the Spleen, Nature New Biology, **231:** 237, (1971).

Forster Stephen C., The Cromolyn Sodium in the Treatment of Vernal Keratoconjunctivitis, Ophthalmology **95:** 194, (1988).

Friedlander, M. and Allansmith, M. R., Ocular Allergy, Annals of Ophthalmology, **7**, 1171, (1975).

Kaseras A.G. and Reuben, M., Aetiology of Keratoconus, Br. Med. Journal, **60:** 522, (1976).

Kimura S.J. and Thygeson P., The Cytology of External Ocular Disease, Am. Journal of Ophth., **39:** 137, (1955).

Lanier B.Q., Tremblay N. and Smith J.P., Double Masked Comparison of Ocular Decongestants as Therapy for Allergic Conjunctivitis, Annals of Allergy (Abstract), **50:** 176, (1983).

Morehead, R.P., Human Pathology, McGraw Hill, (1965).

Morgan G., The Pathology of Vernal Keratoconjunctivitis, Trans. Ophth. Soc. UK, **91:** 467, (1971).

Mtanda A.T. and Sangawe J.F., Cryosurgery in Vernal Catarrh, Tropical and Geographical Medicine, **35:** 381, (1983).

Neumann E., Second Season Prednisolone Treatment in Vernal Conjunctivitis with Special Reference to Corneal Complications, Br. Journal of Ophth., **42:** 674, (1958).

Rahi A. and Garner A., Immunology of the Eye, Oxford Blackwell, (1976).

Roit I., Essential Immunology, (2nd Ed.), Blackwell Scientific Publication, Oxford, (1974).

Sharma P. and Gupta S.K., Clinical and Pharmacological Evaluation of Disodium Cromoglycate in the Management of Vernal Keratoconjunctivitis, IRCS Med. Sci., **13:** 857, (1985).

Shuler J., Levenson J. and Mondino, B., Inferior Corneal Ulcers Associated with Palpebral Vernal Conjunctivitis, Am. Journal of Ophth., **106:** 106, (1988).

Smith J.B. and Willis A.L., Aspirin Selectivity Inhibits Prostaglandin Production in Human Platelets, Nature New Biology, **231:** 235, (1971).

Srinivasan B.D., Jacobiec, F. A. and Iwamoto, T., Giant Papillary Conjunctivitis with Ocular Prosthesis, Arch. of Ophth., **97**, 892, (1979).

Sugar S.H., Tarsectomy for Proliferative Palpebral Vernal Conjunctivitis, Am. Journal of Ophth. **51:** 429, (1962).

Takakusaki I., Fine Structure of the Human Palpebral Conjunction with Special Reference to the Pathological Changes in Vernal Conjunctivitis, Arch. Histol. Jap., **Vol. 30**, No. 3, 247, (1969).

Trocme S., and Allansmith M.R., Conjunctival Deposition of Eosinophil Granule Major Basic Protein in Vernal Kerato-conjunctivitis and Contact Lens Associated Giant Papillary Conjunctivitis, Am. Journal Ophth. **108:** 57, (1989).

Tse D.T., Baervedt G. and Mandelbaum S., Mucous Membrane Grafting for Severe Palpebral Vernal Conjunctivitis, Arch. Ophth., **101:** 1879, (Abstract), (1983).

Udell I.J., Gleich G.J., Allansmith M.R. and Allansmith M.B., Eosinophil Granule Major Basic Protein and Charcol-Leyden Crystal Protein in Human Tears, Am. Journal of Ophth., **92:** 824, (1981).

Vane J.R., Inhibition of Prostaglandin Synthesis as a Mechanism of Action for Aspirin-Like Drugs, Nature New Biology, **231:** 232, (1971).

Vanghan D., General Ophthalmology, Lange Medical Publications, California (1980).

Wedd, J.E., Awarado, J. A. and Hogan, M. J., Histology of the Human Eye, WB Sanders, (1971).

Wells J.V., Immune Mechanisms in Tissue Damage, in: Basic and Clinical Immunology, (4th Ed.), Lange Medical Publications, California, (1982).

Wolff, E., Anatomy of the Eye and the Orbit, 6th Edition, London Lewis, (1968).

Yanoff M. and Fine B., Ocular Pathology, 1st Edition, Harper and Row, (1975).

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