EFFECT OF ACETYLSALICYCLIC ACID (ASPIRIN®) AND DEXAMETHAZONE ON VERNALCONJUNCTIVITIS - A COMPARATIVE ANALYSIS

BY

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ABSTRACT

Vernal conjunctivitis is a common external eye disease, particularly amongst children and young adults, characterized by severe itching, papillae formation and brownish colouration of the eyes among others. Various treatment modalities are available with their various side effects. A six-week open study was carried out to evaluate the effect of Aspirin® and Dexamethazone in the treatment of vernal conjunctivitis. Twenty four patients with a mean age of 12.42±5.77 years were included in the study. The patients were divided into four groups A, B, C, D. Group A had a combined therapy of Aspirin® and Dexamethazone (Maxidex 0.1% of eye drop); Group B had Aspirin therapy with Placebo drops (Normal saline); Group C had Dexamethazone therapy alone while Group D had Placebo drops only. A marked improvement of the clinical features of vernal conjunctivitis, namely itching, limbal or tarsal papillae, conjunctival or scleral discoloration were noted within 6 weeks in group A, B and C while the control group, D showed no improvement. Thus Aspirin® and Dexamethazone reduced significantly the clinical features of vernal conjunctivitis. Using the t-test at $p<0.05$, $p<0.01$ and $p<0.001$, a comparative analysis was done and no significant difference in efficacy was found in groups A, B and C. Therefore, Aspirin and Dexamethazone are comparable in action in the therapeutic management of vernal conjunctivitis and aspirin can be used as the only treatment option in patients that can tolerate its use.

KEYWORDS: Aspirin®, vernal conjunctivitis, dexamethazone, itching, papillae, conjunctival discolouration.

INTRODUCTION

Inflammation of the conjunctiva (conjunctivitis) is a common eye disease. The source is usually exogenous, sometimes endogenous. Allergic conjunctivitis refers to the conjunctivitis due to hypersensitivity of the conjunctiva to foreign substances and is characterized by discharge, redness, itching, irritation, swelling, sunlight sensitivity and tearing. Allergic conjunctivitis can be sub-classified into: vernal conjunctivitis, phlyctenular conjunctivitis and allergic conjunctivitis secondary to drugs.

Vernal conjunctivitis is a severe form of bilateral allergic conjunctivitis that occurs worldwide, but it is seen most frequently in warm climates. It is also referred to as seasonal or warm weather conjunctivitis. It is a perennial problem and affects all classes of people, it is sporadic and non-contagious. It is less common in temperate than in warm climates and it's almost non-existent in cold climates. It is almost always more severe during spring, summer and fall than in winter. In the cooler months, the condition subsides and gives no trouble although lesion persist, the symptoms reoccur with the return of heat. This condition is most common in children and young adults with incidence decreasing after about 15 years of age[1]. It is rarely seen before 3 years of age or after the third decade. The incidence is higher in males than in females with a ratio of 2 to 1[1]. It is characterized by severe itching, papillae, brownish discolouration of the eyes, lacrimation and occasional photophobia, foreign body sensation with resulting blepharospasm and white ropy secretions are also seen. The etiology is uncertain because no specific allergen has been identified in the pathogenesis of vernal conjunctivitis, but causative factor is predicted on exposure to allergens in the environment. In a majority of the patients with vernal conjunctivitis, they show allergy to pollens and usually have an associated family history of atopy; a history of infantile

eczema, allergic rhinitis or asthma has been reported in 74-85% of vernal conjunctivitis patients[2]. Vernal conjunctivitis is a seasonal type I hypersensitivity reaction.

Various treatment modalities have been instituted based on the severity and associated signs and symptoms of the reaction.

I. Antihistamines: Topical (often in combination with vasoconstrictors e.g. Antistin-privin) and oral antihistamine e.g. piriton are widely used.
II. Corticosteriod are effective immunosuppressive agents. They are synthetic derivatives of those naturally occurring within the adrenocortical system. Steroids such as prednisolone and Dexamethazone, work by suppressing or preventing the inflammatory response of a hypersensitivity reaction.
III. Cromolyn sodium (disodium cromoglycate) has been shown to inhibit the release of chemical mediators by mast cells. It is a mast cell stabilizer.
IV. Cryotherapy is another treatment option. Here cold therapy is applied to the eyes and is mostly indicated when there is marked hypertrophy with cobblestones in the tarsal conjunctiva.
V. Aspirin® is a nonsteroidal anti-inflammatory drug. It also has antipyretic and analgesic effects. It is a weak organic acid. Aspirin® has a long history of use and availability without prescription. Its use up to the present day is because of its low cost and long history of safety.

Ciprandi *et al*[3] evaluated the topical use of acetylsalicylic acid (ASA) eye drops (1% solution) compared to placebo in the treatment of patients with seasonal allergic conjunctivitis. The ASA treated group improved significantly compared to the placebo treated group and no serious side effects were observed.

Sankarkumar T. *et al*[4] used cryotherapy of the palpebral conjunctiva with oral aspirin in mixed type active vernal kerato-conjunctivitis. Patients received oral Aspirin 0.50 to 1.50g in three divided doses daily over six weeks and the result showed that the relief from symptoms was statistically significant ($p<0.001$) and objective improvement (palpebral and bulbar signs) also was statistically significant ($p<0.001$).

Chaudhary[5] evaluated the combined use of systemic aspirin and cromolyn sodium in intractable vernal catarrh, with 11 patients with intractable vernal keratoconjunctivitis of mixed type with limbal predominance. The combined therapy showed a significant improvement in itching, lacrimation, and limbal edema ($p<0.05$) and improved photophobia, palpebral lesions and corneal staining ($p<0.05$) at six weeks. In another study by Srininvas[6] using patients with vernal conjunctivitis, divided into groups A and B who received Aspirin® and cromoglycate, 2% eye drops respectively. The result showed that aspirin and cromoglycate showed encouraging results.

The purposes of this study were to determine the effects of oral Aspirin® and topical Dexamethazone therapy in the management of vernal conjunctivitis; both individually and in combination of the two drugs.

METHOD

The research was an open prospective study in which 24 patients aged 3-21years (mean age 12.42±5.77years) presenting with the clinical features of vernal conjunctivitis were enrolled. The patients were randomly divided into four groups, A, B, C and D and with no gender discrimination. The effects of Aspirin® Dexamethazone on vernal conjunctivitis were compared. The instrument of research was direct tests in the clinic, questionnaires and basic examination sheet and the research materials used were pen torch, hand magnifier and ophthalmoscope.

Clinical features were evaluated and data collected at the start, two weeks during drug administration, four weeks and at six weeks. This was done at the eye clinic Central Hospital Benin City, Nigeria. The patients were treated throughout the six weeks duration except those in group D that were given placebo drops.

The clinical features of vernal conjunctivitis, namely; limbal or tarsal palpillae, conjunctiva or scleral discolouration and ocular itching were used and graded according to degree of severity on a scale of 0 to 3. The gradings were:

0 - when no clinical feature was present.
1 - when clinical features were mild.
2 - when clinical features were moderate.
3 - when clinical features were severe.

Patients group A had combined therapy of Aspirin® and Dexamethazone (0.1% Maxidex), Group B combined Aspirin® tablets and Placebo drops, Group C Dexamethazone (0.1% Maxidex) drops only and Group D Placebo drops only (normal saline). The dosage of Aspirin® oral tables was 0.50-1.50g in divided doses per day depending on age. The Dexamathazone (0.1% Maxidex) and Placebo drops were administered 1 drop, four times daily for six weeks.

Patients included in the study were screened for bleeding tendency and gastritis. Children with bronchial asthma were not included in the study, as well as those with suspected glaucoma and cataract. Patients on tablets Aspirin were advised to take the drug after meals with adequate water. All patients were strictly monitored to ensure strict compliance.

The two tailed t-test was used for data analysis in testing the difference between means.

DISCUSSION

Vernal conjunctivitis is a type I immediate hypersensivity reaction. The body's immune system reacts to foreign substances (Allergens), which the body perceives as a potential threat. This response can be innate or acquired. The presence of an allergen on the conjunctiva initiates two simultaneous immune responses. One response is due to the release of the "preformed"inflammatory mediators like histamine from the mast cells and the other response is caused by the production of Arachidonic acid and its conversion into the "newly-formed" mediators like prostaglandins. "Preformed" mediators are released immediately upon exposure, while the "newly-formed" mediators are delayed for roughly 8-24 hours. The allergen attracts and gets bound to an antibody called immunoglobulin E (IgE), this forms the antibody-Antigen complex and then adheres to mast cells and leads to the degranulation of the mast cells. This causes the discharge of the "preformed" mediators. Mediators like Histamine and bradykinin released immediately, stimulate the nerve endings, called nociceptors, leading to the sensation of itching. Both mediators also increase the vascular permeability and vasodilation causing the redness and conjunctival injection. Other mediators released by the mast cells send out chemical signals, which attract both erythrocytes and leucocytes to the area. The other defense mechanism of the body that produces newly formed inflammatory mediators is referred to as the Arachidonic acid cascade. The newly formed mediators are prostaglandins, thromboxanes and leukotriene, - these are collectively called the Eicosanoids.

Aspirin®, (acetyl salicylic acid, ASA) has a pka of 3.5. It is an effective anti-inflammatory drug. Aspirin is rapidly absorbed from the stomach and upper small intestine, yielding peak plasma level within 1-2 hours. The acid medium in the stomach keeps a large fraction of the aspirin in the non-ionized form promoting absorption. The effectiveness of Aspirin is due partly to its ability to inhibit cyclo-oxygenase and partly to the effect of its primary metabolite, salicylate, both to inhibit cyclo-oxygenase and to act in other ways i.e. as an oxygen radical scavenger. Aspirin® as such, irreversibly blocks the enzyme cyclo-oxygenase (prostaglandin synthase) which catalyzes the conversion of Archidonic acid to endoperoxide compounds.

In addition to reducing the synthesis of eicosanoid mediators, ASA also interferes with the chemical mediators of the kalikrein system. As a result, aspirin inhibits granulocyte adherence to damaged vasculature, stabilizes lysosomes and inhibits the migration of polymorphonuclear leukocytes and macrophages into the site of inflammation. Aspirin® is therefore a non steroidal anti-inflammatory drug with anti-prostaglandin effect.

In this study, 24 patients, 18 male (75%) and 6 female (25%) making a ratio of 3:1 and an age range of 3-21 years (mean age 12.425.77) were recruited. These patients were randomly selected into four groups. D group was placed on placebo drops, C group had Dexamethazone only, B group had Aspirin® and placebo drop and A group had Dexamethazone drop and Aspirin® tablets.

The clinical features of papillae, colour and itching were used for assessment. For group A, the mean for papillae, colour and itching were 1.17±0.37 respectively before the use of Dexamethazone and Aspirin® tablets. These values decreased to 0.17±0.37 for papillae and

colour while the value for itching was 0.50±0.05 at the end of two weeks of treatment. The clinical features were eliminated (mean 0.00±0.00) at the end of six weeks of treatment (table 1). With a two tailed t-test at $p<0.005$, $p<0.01$ and $p<0.001$, a significant difference was found with the values before and after treatment. This was in addition found to agree with the works of Ciprandi *et al*[6] and Srinivas[7].

In group B the mean value for papillae colour and itching was 1.50±0.50 respectively before treatment; and after treatment, this reduced to 0.50±0.50 for papillae and colour while the value for itching reduced to 0.67±0.47 at the end of two weeks. These clinical features were also eliminated (mean 0.00±0.00) at the end of six weeks of treatment with Aspirin® and Placebo (Table 2). Also, a two tailed t-test was done at $p<0.05$, $p<0.01$, and $p<0.001$ which gave a significant difference between the means before and after treatment. This finding was in agreement with the work of Ciprandi *et al*[8] and Meyer *et al*[9] who reported the efficacy of anti-prostaglandin therapy in vernal conjunctivitis.

In group C, the mean value of papillae and itching was 1.33±0.47, while that of colour was 1.16±0.50 before treatment. There was a reduction of these values at the end of two weeks treatment to 0.33±0.047 for papillae and colour while that for itching reduced to 0.67±0.47. Also at the end of six weeks treatment with Dexamethazone all the clinical features were eliminated (mean 0.00±0.00, table 3). The two tailed t-test was done at $p<0.05$, $p<0.01$, and $p<0.001$ and a significant difference was found between the mean before and after treatment. This agreed with the works of Amaechi[10] and Ronald *et al*[11]. They reported a positive effect of steroids on vernal conjunctivitis.

For group D, the mean value for papillae and itching was 1.50±0.50 while that for colour was 1.33±
0.47 before treatment with placebo (saline solution) they remained largely the same throughout the duration of study. Placebo was not really a treatment option but a control.

Aspirin® was found to decrease the clinical features of vernal conjunctivitis in children and young adult. Meyer *et al*[9] used patients who remained symptomatic after treatment with steroid and opticrom drops topically and recorded 88.88% success rate. Thus from our study a marked improvement was noticed with Aspirin® and consequently aspirin is an additional therapeutic tool in the treatment of vernal conjunctivitis and can be tried as the only treatment in new cases of this disease, in conjunction with tear drop substitutes to help prevent punctate keratopathy by lubricating the cornea. Also the combined therapy of Aspirin® and Dexamethazone gave a significant difference compared to placebo; consequently, there was a fast relief of the clinical features of vernal conjunctivitis, than with placebo drops.

A comparative analysis of the effectiveness of Aspirin® was done with Dexamethazone; the difference between the mean before each treatment was tested using two tailed t-test and no significant difference was found. The mean values after treatment were also the same statistically. Thus there was no significant difference between the use of Aspirin® and Dexamethazone therapy separately. In addition, the analysis of the result of treatment with Dexamethazone and combined therapy of Dexamethazone and Aspirin® gave no significant difference and so there was no significant difference between treatment with Dexamethazone only or combined therapy with Dexamethazone and Aspirin®.

Corticosteroids are phospholipase inhibitors, preventing the metabolism of phospholipids in the cell membranes to Arachidonic acid, thus preventing the release of leukotrienes, and prostacyclin, limiting the inflammatory response. Aspirin® on the other hand, is cyclo-oxygenase inhibitor, inhibiting the release of prostaglandins, thomboxanes and prostacyclin; ultimately too limiting the inflammatory response.

From the result of this present study, the use of Dexamethazone and Aspirin® were effective in the management of vernal conjunctivitis. Consequently, both treatment modalities can be used separately as there was no potentiation of their efficacy with combined use. Finally, Aspirin® can be used as the only treatment especially in new cases of the disease in conjunction with artificial tear drops for adequate corneal lubrication.

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TABLE 1: GRADE SCORE FOR PAPILLAE (P), SCLERAL DISCOLOURATION (C) AND ITCHING (I) BEFORE AND AFTER USE OF DRUGS FOR GROUP A.

Before Treatment			During treatment								
			2 weeks			4 weeks			6 weeks		
P	C	I	P	C	I	P	C	I	P	C	I
1	1	1	0	0	1	0	0	1	0	0	0
2	2	2	0	0	1	0	0	1	0	0	0
1	1	1	1	1	1	0	0	1	0	0	0
1	1	1	0	0	1	0	0	0	0	0	0
1	1	1	0	0	0	1	0	0	0	0	0
1	1	1	0	0	0	0	0	0	0	0	0
1.17 ± 0.37	1.17 ± 0.37	1.17 ± 0.37	0.17 ± 0.37	0.17 ± 0.37	0.50 ± 0.50	0.00 ± 0.00	0.00 ± 0.00	0.50 ± 0.50	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

TABLE 2: GRADE SCORE FOR PAPILLAE (P), SCLERAL DISCOLOURATION (C) AND ITCHING (I) BEFORE AND AFTER USE OF DRUGS FOR GROUP B.

Before Treatment			During treatment								
			2 weeks			4 weeks			6 weeks		
P	C	I	P	C	I	P	C	I	P	C	I
2	2	2	1	1	1	0	0	1	0	0	0
1	1	1	0	0	0	0	0	0	0	0	0
2	2	2	1	1	1	0	0	1	0	0	0
2	2	2	1	1	1	0	0	1	0	0	0
1	1	1	0	0	0	0	0	0	0	0	0
1	1	1	0	0	1	2	0	0	0	0	0
1.50 ± 0.50	1.50 ± 0.50	1.50 ± 0.50	0.50 ± 0.50	0.50 ± 0.50	0.67 ± 0.42	0.00 ± 0.00	0.00 ± 0.00	0.50 ± 0.50	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

TABLE 3: GRADE SCORE FOR PAPILLAE (P), SCLERAL DISCOLOURATION (C) AND ITCHING (I) BEFORE AND AFTER USE OF DRUGS FOR GROUP C.

Before Treatment			During treatment								
			2 weeks			4 weeks			6 weeks		
P	C	I	P	C	I	P	C	I	P	C	I
2	2	2	1	1	1	0	0	1	0	0	0
1	0	1	0	0	1	0	0	1	0	0	0
1	1	1	0	0	0	0	0	0	0	0	0
1	1	1	0	1	1	0	0	0	0	0	0
1	1	2	0	0	0	0	0	0	0	0	0
2	2	2	1	1	1	0	0	1	0	0	0
1.33 ± 0.47	1.16 ± 0.50	1.33 ± 0.47	0.33 ± 0.47	0.33 ± 0.47	0.67 ± 0.47	0.00 ± 0.00	0.00 ± 0.00	0.50 ± 0.50	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

TABLE 4: GRADE SCORE FOR PAPILLAE (P), SCLERAL DISCOLOURATION (C) AND ITCHING (I) BEFORE AND AFTER USE OF DRUGS FOR GROUP D.

Before Treatment			During treatment								
			2 weeks			4 weeks			6 weeks		
P	C	I	P	C	I	P	C	I	P	C	I
2	1	2	2	1	2	2	1	2	2	1	2
1	1	1	1	1	1	1	1	1	1	1	1
2	2	2	2	2	2	0	2	2	2	2	2
1	1	1	1	1	1	2	1	1	1	1	1
2	2	1	2	2	2	0	2	2	2	2	2
1	1	1	1	1	1	1	1	1	1	1	1
1.50 ± 0.50	1.33 ± 0.47	1.50 ± 0.50	1.50 ± 0.50	1.33 ± 0.47	1.50 ± 0.50	1.50 ± 0.50	1.33 ± 0.47	1.50 ± 0.50	1.50 ± 0.50	1.33 ± 0.47	1.50 ± 0.50