Analysis of the role of tear substitutes in the eye relieve in chronic seasonal allergic conjunctivitis

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Abstract: Aim: To evaluate the efficacy of tear substitute in achieving the eye relieve and comfortability in patients with chronic seasonal allergic conjunctivitis i.e. Spring catarrh and analysis of the outcome results. **Design:** Prospective randomized study. **Patients and method:** 240 patients with seasonal allergic conjunctivitis complicating with dry eye are randomized in 3 groups. Group I received antihistaminic in the form of Epinastine hydrochloride 0.5 mg per mL (Relestat®, Allergan®) twice daily in between the attacks while group II received tear substitutes in the form of Carboxymethylcellulose and glycerin (Optive®, Allergan®) twice daily, while group III received combination of the two drugs. All patients gave complete history and examined as regard visual acuity, refraction, IOP, slit lamp examination, tear film break up time (BUT) and Schirmer test. The outcome measures were the eye comfortability and relieve in the form of relieve of eye burning and blurring , reduction in signs of the allergic conjunctivitis especially the eye redness. **Results:** 240 patients with mean age 16.3±2.4 years. Female to male ratio was 1:1. 40 patients were excluded from the study mainly due to non compliance. Complete patient comfortability in 46.5% of patients and partial comfortability in 33.8% of patients. These percent to 60.6% and 21.3% respectively if antihistaminic were added to tear substitutes. Relieve of burning sensation, tear substitutes alone can achieve this in 53 (74.6 %) patients and in 52 (85.2%) of patients if antihistaminic was added. **Conclusion:** Chronic allergy and dry eye are two faces of the same coin. At a time, allergy may fade away but dry eye persists .The patient with chronic allergy will never feel complete eye relieve except with addition of tear substitutes. Patients should continue tear substitutes during the attack. It is advised that if the ophthalmologists wants to prescribe a single drug for follow up use to the chronic allergic patient, the drug of choice is tear substitutes. Dry eye disease is the missing already present disease in chronic allergy. This study advisd that patients with chronic allergy should avoid exposure to sun, wind, dust or smoke in order not to aggrevate dry eye. This study proved that tear substitutes perscription in chronic allergy not only achieve eye relieve but also improve the quality of vision. Till now, the chronic allergy-dry eye complex is still unfinished business and further studies are needed to solve the chronic allergy-dry eye puzzple.
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Key Words: Allergy, tear substitutes, eye relieve.

1. Introduction

Allergic diseases have dramatically increased in the last decades [1-4]. Ocular allergy represents one of the most common ocular conditions encountered in clinical practice. A single cause of this increase cannot be pinpointed and experts are therefore considering the contribution of numerous factors, including genetics, air pollution in urban areas, pets, and early childhood exposure [5]. The associated costs have increased substantially as more of the population require treatment for allergies [6].

Allergic conjunctivitis is an inclusive term that encompasses seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), and atopic keratocongiuntivitis (AKC). However, AKC and VKC have clinical and pathophysiological features quite different from SAC and PAC, inspite of some common markers of allergy [7].

Also contact lenses or ocular prosthesis associated giant papillary conjunctivitis (GPC) are often included in the group of ocular allergy, however they should not be considered as real allergic diseases, but as chronic ocular micro-trauma related disorders, which need to be managed by ophthalmologists in association with contact lenses experts [8].

Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are the most common forms of ocular allergies. Estimates vary, but these types of allergy are said to affect at least 15–20% of the population [9]. The presence of specific IgE antibodies to diagnostic features of SAC and PAC consist of itching, redness, and swelling of the conjunctiva. Redness, or conjunctival injection, tends to be mild to moderate. Conjunctival swelling, or chemosis, tends to be moderate, and somewhat more prominent than one would expect for a mild amount of redness. Itching is a fairly consistent symptom of SAC and PAC. Corneal involvement is rare [6].

As regard treatment, Corticosteroids remain among the most potent pharmacologic agents used in the more severe variants of ocular allergy and are also effective in the treatment of acute and chronic forms of AC [10-13]. But They have some limitations, including ocular adverse effects, such as delayed wound healing, secondary infection, elevated intraocular pressure, and formation of cataract. These agents are therefore appropriate for short courses; however, if needed for longer durations, an eye examination should be carried out, including baseline assessment of cataracts and intraocular pressure measurement [3].

Dry eye is one of the most frequently encountered ocular morbidities, a growing public health problem and one of the most common conditions seen by eye care practitioners.[15] In the light of new knowledge about the roles of ocular surface inflammation and tear hyperosmolarity in dry eye and the effects of dry eye on visual function, the International Dry Eye Workshop (DEWS) defined dry eye as a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface".[16]

Dry eye syndrome is also defined as any disturbance in tear film physiology that leads to a clinically evident drying of the ocular surface. Although an actual diagnosis of primary dry eye may be less common, mild to moderate dry eye is thought to occur in 11-22% of the general population [14].

Aim:

To evaluate the efficacy of tear substitute in achieving the eye relieve and comfortebility in patients with chronic seasonal allergic conjunctivitis i.e. Spring catarrh and analysis of the outcome results.

Design: Prospective randomized study.

2.Patients and method:

A total of 240 patients with seasonal allergic conjunctivitis complicating with dry eye are randomized in 3 groups. Group I received antihistaminic in the form of Epinastine hydrochloride 0.5 mg per mL (Relestat®, Allergan®) twice daily in between the attacks while group II received tear substitute in the form of Carboxymetylcellulose and glycerin (Optive®, Allergan®) twice daily , while group III received combination of the two drugs. All patients gave complete history and examined as regard visual acuity, refraction, IOP, slit lamp examination, tear film break up time (BUT) and Schirmer test. The outcome measures were the patient eye comfortability and relieve in the form of relieve of eye burning and blurring , reduction in signs of the allergic conjunctivitis especially the eye redness.

Study Design

This randomized, single-masked, active-controlled, parallel group study Included in this study were patients aged 12 years or older who were diagnosed with acute SAC and relieve the acute attack before the start of the study. Patients with acute attack or developed acute attack during the study period were excluded. Acute attack means severe itching, photophobia, severe conjunctival injection and all these relieved by topical steriod therapy. Female patients of childbearing age were included only if a negative urine pregnancy test was observed at the first study visit. Patients participating in any drug or device clinical investigation within 30 days before entry into this study or during the period of study participation, female patients who were breastfeeding, and patients who were not using an approved method of birth control during the study duration were excluded from the study. Also excluded were patients using any of the following drugs 7 days before the first study visit: systemic or ocular H1 antihistamines; H1 antihistamine vasoconstrictor drug combinations; decongestants; monoamine oxidase inhibitors; other topical ophthalmic preparations; prostaglandins or prostaglandin derivatives; and ocular, topical, or systemic NSAIDs. Patients using inhaled, ocular, or topical corticosteroids or mast-cell stabilizers for 7 days, depo-corticosteroids for 45 days, and immunosuppressive agents for 2 months, respectively, before the first study visit were also excluded. Finally, patients who had a known hypersensitivity to the study medications or their components (including benzalkonium chloride) or contraindications to ocular corticosteroids, an intraocular pressure ≥21 mm Hg in either eye or any type of glaucoma, best-corrected distance visual acuity (C Chart decimal) of ≤ 0.5 in either eye, a history of any severe or serious ocular pathology or medical conditions, and those patients unable or unwilling to discontinue wearing contact lenses during the study were also excluded.

Study Treatments and Assessments

Eligible patients were stratified by site and randomly assigned in a 1:1:1 ratio by a computer-generated randomization list to investigator-masked treatment with either Epinastine hydrochloride 0.5 mg per mL (Group I) or Carboxymetylcellulose and glycerin (Group II) or both Epinastine hydrochloride 0.5 mg per mL and Carboxymetylcellulose and glycerin (Group III). Patients randomly assigned were instructed to self-administer 1 drop of Epinastine hydrochloride 0.5 mg per mL T.d.s at approximately 12-hour intervals (group II) or 1 drop

of Carboxymetylcellulose and glycerin (Optive) twice daily at 12- hour interval more (group II), or 1 drop of of both medications 5 minutes apart (group III) in both eyes for 3 months and to record each study medication instillation in a patient diary.

For purposes of masking, labels on the commercial bottles of Epinastine hydrochloride and Carboxymetylcellulose and glycerin were replaced with investigational labels and bottles were packaged in identical kit boxes in an attempt to mask patients.

Patients completed 4 study visits. At visit 1, on the first day of the study, demographic data, and relevant medical and ocular history was collected. Baseline ocular data for signs and symptoms was collected and, if applicable, a urine pregnancy test was conducted on this day. Patient diaries, used to assess study treatment exposure and treatment compliance only, and patient medication kits were provided.

Visit 2 was conducted at the end of the 1st month, visit 3 at the end of the 2nd month and visit 4 at the end of the 3rd month. Data on concomitant medications, visual acuity (VA), ocular symptoms and signs, IOP, and adverse events (AEs) was collected at all study visits.

Tear break up time (BUT) was performed by Fluorescein 2% was instilled into the conjunctival sac, then the patient was asked to blink several times The tear film was examined at the slit-lamp with a broad beam using the cobalt blue filter. After that, black spots or lines appear in the fluorescein-stained film, indicating the formation of dry areas. The BUT is the interval between the last blink and the appearance of the first randomly distributed dry spot. A BUT of less than 10 seconds is abnormal.

The Schirmer test was performed by drying the gently dried of excess tears. Then the filter paper was folded 5 mm from one end and inserted at the junction of the middle and outer third of the lower lid, taking care not to touch the cornea or lashes. The patient was asked to keep the eyes gently closed. After 5 minutes the filter paper was removed and the amount of wetting from the fold was measured. Less than 10 mm of wetting after 5 minutes without anaesthesia and less than 6 mm with anaesthesia was considered abnormal (Figure 1).

Outcomes Measures

Ocular signs and symptoms were assessed at baseline at each study visit thereafter. This is achieved by a quationnaire provided to the patient at baseline and each study visit thereafter. This quationnaire included eye comfortability (complete, partial or no at all), relieve of foreign body (FB) sensation, improvement of burning sensation(yes or no),relieve of blurring of vision, improvement of tearing (yes or no) and mucus strands (present or not and if present improved or not by yes or no). The quationnaire also included signs e.g. counjuctival injection, IOP, slit lamp biomicroscopy, BUT and schirmer test.

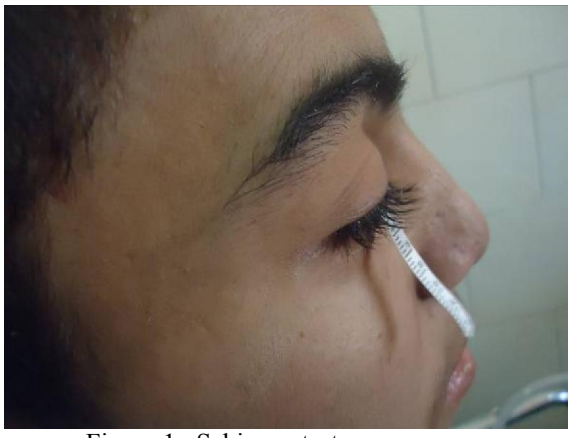

Figure 1 : Schirmer test

Tolerability assessments were based on AEs, VA, biomicroscopy, and IOP measurements. AEs were collected through patient quationnaire or observation. The incidence and type of AEs reported by the patient or observed by the investigator at each study visit were collected from the start to end of the study. VA was measured at all visits using standardized Landolt's chart. The same VA testing method was used for all study visits for each patient. An applanation tonometer was used to measure IOP. Clinically significant IOP increases were defined as ≥10 mm Hg from baseline.

3. Results

Patient Disposition

A total of 240 patients were randomly assigned to group I (n =80) or group II(n=80) or group III (n= 80). 12 patients were excluded from the group I (2 developed attacks and 10 non compliant). 9 patients were excluded from group II (2 developed attacks and 7 were non compliant). 19 patients excluded from group III (4 developed attacks and 15 were non compliant in follow up) figure 2.

Patient Baseline Characteristics

The demographic characteristics of patients in the three groups were similar (Table I).

Table 2 shows the final results of the study. As regards foreign body sensation, it was improved by tear substitutes alone in 48 (67.6%) patients and by tear substitutes and antihistaminic in 55 (90.2%) patients. Mucus strands were found in 54 patients of 200 patients. Of these 54 patients 27 patients were given only antihistaminc and not improved, 11 patients were given tear substitutes alone and 8 (72.3 %) of them improved, 22 patients were given combined therapy and 16 (72.3 %) of them improved.

Regarding the tear break up time (BUT), it was the same as baseline in patients who were given antihistaminic alone but prolonged with tear substitutes alone in Prolonged in 47 (66.2%) in combination with antihistaminic in 44 (72.1%). Schirmer test improved in 43(60.6%) patients with tear substitues alone and in 36 (59%) if antihistamnic was added.

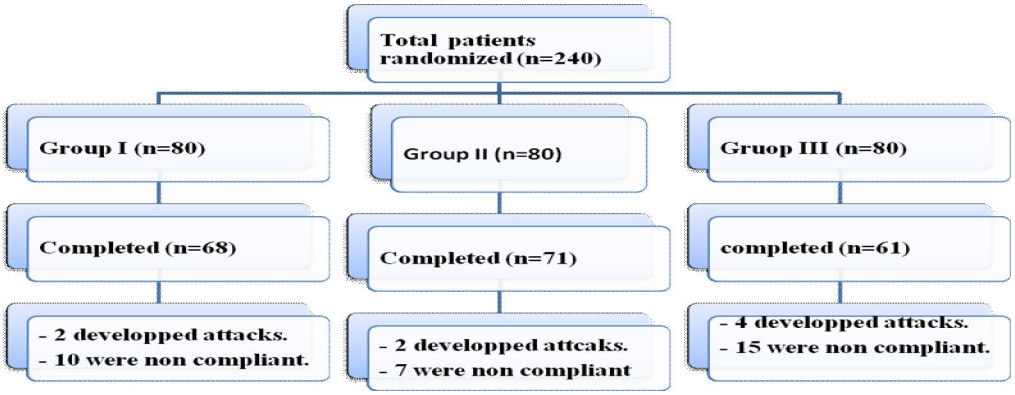

Figure 2: Patient disposition

Table I. Demographic data

Variant	RE Group (n=80)	OP Group (n=80)	BO group (n=80)	Total (n=240)
Age, mean (SD), *y*	15±2.5	16± 1.6	18± 3.1	16.3±2.4
Sex, no. (%) - Males. - Females.	 35(43.8%) 45(56.2%)	 39(48.7%) 41(51.3%)	 46(57.5%) 34(42.5%)	 120(50%) 120(50%)
Occupation: - Farmer. - Workers. - Student. - Others.	 18 (22.5%) 21(26.2%) 31 (38.8%) 10(12.5%)	 15(18.8%) 23(28.8%) 36 (45%) 6 (7.5%)	 12(15%) 26(32.5%) 32(40%) 10(12.5%)	 45 (18.6%) 70(29.2%) 99(41.3%) 26(10.9%)
Residence: - Urban. - Rural.	 35 (43.8%) 45(56.2%)	 41(51.3%) 39(48.7%)	 51(63.8%) 29 (36.2%)	 127 (52.9%) 113(47.1%)

Table 2: Final results.

Complaint	No of patients complaining	Relieve of complaint	Group I (N=68)	Group II (N=71)	Group III (N=61)
Eye discomfortability	200 (100%)	Eye comfortability - Complete - Partial - No	 11(16.2%) 19 (27.9%) 38 (55.9%)	 33 (46.5%) 24 (33.8%) 14 (19.7%)	 37 (60.6%) 13 (21.3%) 11 (18%)
Burning sensation	200 (100%)	Burning sensation relieve	23 (33.8%)	53 (74.6 %)	52 (85.2%)
FB sensation	200 (100%)	FB sensation relieve	25 (35.8%)	48 (67.6%)	55 (90.2%)
Tearing	200 (100%)	Tearing relieve	9 (13.2%)	41(57.7%)	39 (63.9 %)
Mucus discharge	54 (27%)	Decrease of mucus discharge	0\21 (zero %)	8\11 (72.7 %)	16\22 (72.7 %)
Blurring of vision	87 (43.5%)	Relieve of blurring of vision	8/37 (21.6 %)	36/53(67.9%)	43/49(87.8%)
Special tests		Break up time (BUT)	The same as baseline	Prolonged in 47 (66.2%)	Prolonged in 44 (72.1%)
		Schirmer test	The same as baseline	Improved in 43(60.6%)	Improved in 36 (59%)

4.Discussion:-

Seasonal allergic conjunctivitis is a chronic disease so that the patient eye comforability is the target of the physician when prescribing eye drops. To my knowledge, no previous puplished studies concerned with the association of dry eye disease and the chronic allergic conjunctivitis and the role of tear substitutes in achieving the patient eye comfortability. This study concerned with the inbetween attacks of seasonal allergic conjunctivitis and it was found that tear substitutes alone achieved complete patient comfortability in 46.5% of the patients and partial comfortability in 33.8% of patients. These percent to 60.6% and 21.3% respectively if antihistaminic were

added to tear substitutes. This was unlike to Shulman *et al.* who found that Loteprednol etabonate 0.2% as an antihistaminic provided clinically and statistically significant improvement in signs and symptoms of seasonal allergic conjunctivitis [17].Talking about relieve of burning sensation, tear substitutes alone can achieve this in 53 (74.6 %) patients and in 52 (85.2%) of patients if antihistaminic was added. This was unlike to Dell et al. who found that antihistaminic was important to relieve the burning sensation [18]

Blurred vision found in 87 patients of 200 patients (43.5%). Tear subsititutes alone improve this blurring in 36/53(67.9%) Patients These results agreed with Gifford and Ousler who reported that artificial tears provide improvement in eye irritation and blurred vision symptoms, visual contrast sensitivity [19,20].

This study found that a large number of patients were farmers and workers who had prolonged exposure to sun, wind, dust or smoke.

The lowest number of patients who completed the 3 months duration of the study was in group III, which might be due to that those patients felt well and did not come to the follow up visits so best results were obtained in this group.

5. Conclusion:-

Chronic allergy and dry eye are two faces of the same coin. At a time, allergy may fade away but dry eye persists .The patient with chronic allergy will never feel complete eye relieve except with addition of tear substitutes. Patients should continue tear substitutes during the attack. It advised that if the ophthalmologists wants to prescribe a single drug for follow up use to the chronic allergic patient, the drug of choice is tear substitutes. Dry eye disease is the missing already present disease in chronic allergy. This study advisd that patients with chronic allergy should avoid exposure to sun, wind, dust or smoke in order not to aggrevate dry eye. This study proved that tear substitutes prescription in chronic allergy not only achieve eye relieve but also improve the quality of vision. Till now, the chronic allergy-dry eye complex is still unfinished businessand further studies are needed to solve the chronic allergy-dry eye puzzple.

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