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A Double-Masked Comparison of Vitamin A (Retinyl Palmitate) versus Hydroxychloroquine in the Treatment of Dry Eye

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Abstract: ***This study was carried out to compare the efficacy of Retinyl Palmitate with Hydroxychloroquine in the treatment of dry eye. Two groups of dry eye diagnosed patients were taken for study- group A: 20 patients received 0.05% Retinyl Palmitate eye drops and Group B: 20 patients received Hydroxychloroquine. This study was conducted in Ophthalmology Department, Rajindra Hospital, Patiala. Patients fulfilling the inclusion criteria and after verifying the exclusion criteria were enrolled in the study. The main outcome measures were comparison of Schirmer test, Tear film Break up Time Test (TBUT) and OSDI score within and between the groups at each follow up.***

Keywords: Hydroxychloroquine, OSDI, Retinyl Palmitate, Schirmer test, Tear film break up time

1. Introduction

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.[1] Dry eye is a disorder of tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface i.e. exposed ocular surface and is associated with symptoms of ocular discomfort. The tear film not only keeps the surface of the eyes moist but also acts as an important optical medium and prevents from damages that take place due to trivial trauma to eye. [2] 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. [3]

1.1 Epidemiology

Dry eye disease is seen with increased prevalence in patients with autoimmune diseases [4], which affect approximately 8% of the population, of whom 78% are the women. [5] Dry eye disease also effects postmenopausal women [6] and the elderly [7-8]. The prevalence of DED is estimated to be 7.4% to 33.7% [8-9] depending on which study is cited, how the disease is diagnosed, and which population is surveyed. The Beaver Dam population-based study found the DED prevalence rate to be 14% in adults 48 to 91 years of age.[7] The study also found that DED affects more women than men (16.7% versus 11.4% respectively).

1.2 Pathophysiology

Over the past few years, new concepts of pathogenesis have shown that dry eye seems to be caused by inflammation mediated by T-cell lymphocytes. Any disease or dysfunction of the lacrimal functional unit (consisting of lacrimal gland, superior and Inferior lacrimal puncta, lacrimal sac and nasolacrimal duct) disrupts the delicate balance between secretion and degradation of tear components on the ocular surface which destabilizes the tear film with delayed clearance that causes ocular irritation and epithelial abnormalities leading to DED.[10] Any condition which results in rapid stimulation of the lacrimal gland functional unit (e.g. due to dryness) will induce neurogenic inflammation within lacrimal gland acini and activation of T-cells and pro inflammatory cytokines.[11-12]

Primary SS (pSS) is a chronic inflammatory autoimmune disorder leading to dryness of eyes and mouth related to a reduced lacrimal and salivary gland function. This is referred to as sicca symptoms. [13]

1.3 Symptoms

Common Dry Eye Disease[DED] symptoms are Dry, scratchy, gritty or sandy feeling, foreign body sensation, pain or soreness, burning ,itching and increased blinking.[14] Two complaints provide important clues that patients may be suffering from dry eye: exacerbation of irritation by environmental stress and exacerbation of irritation that require prolonged visual attention.[15] The ocular surface disease index [OSDI] permits quantification of common symptoms and provide reasonably objective approach to the evaluation of symptom over them. It is valuable tool in clinical treatment trials.[16]

Dry eye classified according to the clinical severity into three grades [17]:

Grade 1 or mild: Patient have symptom of dry eye but no signs on slit lamp examination. However, other electrophysiological or invasive tests such as hyperosmolarity, hyperlysozyme or inflammatory cytokines may be positive.

Grade 2 or moderate: In addition to symptoms, patient has reversible slit lamp signs such as epithelial erosion, punctate keratopathy, filamentary keratitis, short tear film break up time.

Grade 3 or severe: The patient has, besides the symptom of ocular dryness, signs that have permanent sequel such as corneal ulcer, corneal opacity, corneal neovascularization or squamous epithelial metaplasia.

1.4 Treatment

The treatment of dry eye can be done with:

1) The mainstay first-line therapy is artificial tear substitutes which enhances tear film stability and increase TBUT; however, found to only temporarily relieve the symptoms of dry eye [18] rather than to heal the ocular surface or treat the underlying cause of the disease.
2) Anti-inflammatory therapy :
   - Corticosteroids – Topical corticosteroids can be used in order to decrease ocular surface inflammation inhibiting MMP's, inflammatory cytokines and adhesion molecule production.
   - Tetracyclines inhibit MMPs and IL-1 production [19-20]. Orally administered they decrease ocular surface symptoms in patients with ocular rosacea [21-22] and in patients with recurrent corneal epithelial erosions.
   - Cyclosporin A can be used for long term without presentation of adverse effects characterizing the other anti-inflammatory agents.
3) Vitamin A: It is an important vitamin which would be vital to health of the ocular surface especially the conjunctival epithelium. It is known to regulate the proliferation and differentiation of corneal epithelial cells and preserved conjunctival goblet cells and has been used in the treatment of disease such as dry eye.[23] Some animal experiments proved an additional vitamin A has the ability to increase the conjunctival goblet cell density, which results in more secretion of mucins in tears, thus helping the stability of tear film.[24]
4) Hydroxychloroquine: It is an oral immunomodulator used at a dose of 6-7mg/kg per day in treatment of various autoimmune diseases. It's mechanism of action is attributed to interference with macrophage processing of antigens interfering with T-cell activation[25] and possibly preventing epitope spreading for antibodies. It shows an improvement of the lacrimal function [26]. In addition, HCQ showed favourable effects in children.[27]

2. Materials and Methods

All patients had dry eyes on enrollment. Diagnosis of dry eye was made clinically according to the commonly accepted criteria. After getting clearance from the ethical committee, written informed consent was taken from the patients. Complete general, physical and ophthalmological examinations including color vision and dilated fundus examination to see signs of Hydroxychloroquine toxicity were done. They were advised to discontinue all topical and oral allergic drugs for 2 weeks. After 2 weeks the patients were examined and their baseline signs and symptoms are recorded and were randomly assigned to one of the two study groups:

Group A- Retinyl Palmitate 0.05% QID, preservative free artificial tears for 12 weeks
Group B – Hydroxychloroquine 400mg daily, preservative free artificial tears for 12 weeks
Follow up- monthly (3 month with treatment and 3 month after withdrawal of drugs). The main outcome was measured in terms of:

1. **Schirmer test- It** measures aqueous tear production, performed using Schirmer paper strip made from Whatman no 41 filter paper, 5mm wide, 35mm long which will be kept at lateral lower conjunctival sac. The strip will be removed after 5 minutes and the length of the moistened area will be noted. There are two ways to perform this test: a) Schirmer test I is performed without topical anesthesia, which evaluates better he ability of the ocular gland to respond to ocular stimulation; b) Schirmer test II (or Basic Secretion test) which is performed after topical anesthesia, evaluating better the basal tear secretion. Schirmer test value of less than 10mm in 5 minutes will be diagnosed as dry eye.

2. **Tear film break up time**. Flourescein dye will be instilled by wetting flourescein impregnated paper strip with a drop of saline and placing on the bulbar cornea for a brief moment. After 1 to 2 blinks tear film makes a uniform flourescein green appearance. Patient will be asked not to blink for 60 seconds. The time elapsed between a complete blink and the appearance of first dark spot/streak will be measured and taken to be the break up time. 5 successive measures will be taken and the mean value will be calculated. Normal finding is 10 seconds and more, moderate dry eye is 6-9 seconds and advanced is less than 5 seconds.

3**. OSDI** (Ocular surface disease index)-OSDI is assessed on scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI is a valid and reliable instrument for measuring dry eye disease severity.

Normal : 0-12 points
Mild : 13-22 points
Moderate: 23-32 points
Severe : 33-100 points

3. Results

40 patients of Dry eye presenting to our institute were enrolled into this study with mean age in Group A (45.20 ± 3.665) and Group B (45.70 ± 3.600). The difference in the mean age of both the groups was stastically insignificant (p=0.666)

Female patients were 23 in number and male patients were 17 in number.

There was no statistical difference in between the pre interventional visual acuity (p=0.227) and post interventional visual acuity (p=0.884) in both the groups.

Table 1

		Group A Retinyl palmitate (n=20)	*Group B hydroxychloroquine (n=20)*	*p value*
Age (years)	Mean ± SD	45.20 ± 3.665	45.70 ± 3.600	0.666
Gender Male	Number	9	8	0.749
	% within gender	52.9%	47.1%	
	% within group	45.0%	40.0%	
Female	Number	11	12	
	% within gender	47.8%	52.2%	
	% within group	55.0%	60.0%	
Pre interventional visual acuity	Mean ± SD	0.19840 ± 0.203209	0.13060 ± 0.140495	0.227
Post interventional visual acuity	Mean ± SD	0.13315 ± 0.109300	0.13940 ± 0.156347	0.884

Schirmer test readings had improved in patients of Group A and became stastically significant at 3 months and were maintained till 6 months of follow up. P value of 0.669 at 0 month to p value of 0.000 at 3and 6 months.

Table 2

	Group	*N*	*Mean*	*Std. Deviation*	*P value*
Schirmer test:	Group A	20	7.8	2.118	0.669
0 month	Group B	20	7.5	2.283	
Schirmer test:	Group A	20	13.5	2.14	0
3 month	Group B	20	9.8	2.167	
Schirmer test:	Group A	20	18.15	2.033	0
6 month	Group B	20	11.65	2.084	

Tear film break up time has increased in Group A patients on Retinyl palmitate and became statically significant at 3 months and were maintained till 6 months of follow up. P value of 0.883 at 0 month to 0.001 at 3 month and p value of 0.000 at 6 month of duration.

Table 3

	Group	*N*	*Mean*	*Std. Deviation*	*P value*
Tear film break up time:0 month	Group A	20	7.15	2.368	0.833
	Group B	20	7.3	2.08	
Tear film break up time:3 month	Group A	20	11.9	2.469	0.001
	Group B	20	9.35	2.159	
Tear film break up time:6 month	Group A	20	13.55	0.945	0
	Group B	20	10.15	2.084	

ODSI score had improved in Group A and became stastically significant at 6 months. P value of 0.735 at 0 month to 0.226 at 3 month and p value of 0.004 at 6 month.

Table 4

	Group	*N*	*Mean*	*Std. Deviation*	*P value*
OSDI Score:0 month	Group A	20	26.95	8.787	0.735
	Group B	20	26	8.826	
OSDI Score:3 month	Group A	20	20.4	8.66	0.226
	Group B	20	23.75	8.565	
OSDI Score:6 month	Group A	20	14.35	8.19	0.004
	Group B	20	22.35	8.331	

4. Discussion

In our study 0.05% Retinyl palmitate causes an improvement in Schirmer test, tear film break up time and decrease in ODSI score. In 2008, a prospective, randomized, controlled parallel group study was conducted by Eun Chul Kim et al [26] to compare the efficacy of Retinyl palmitate and cyclosporine A 0.05% eye drops in treating patients with dry eye disease. A total of 150 patients with defined dry eye participated and reported both Retinyl palmitate and cyclosporine A treatments led to significant improvement in blurred vision, tear film BUT, Schirmer score results and impression cytologic findings in patients with dry eye syndrome. In our study, Retinyl palmitate shows an improvement in dry eye disease. In 2016, a double blind randomized control study was conducted by Yoon CH et al[27] to study the effect of hydroxychloroquine treatment on dry eye in subjects with primary Sjogren's syndrome in which patients received 300mg of HCQ or placebo once daily for 12 weeks and were evaluated at baseline 6 and 12 weeks and concluded that flourescein staining score, Schirmer test score didn't differ significantly.HCQ at 300mg daily for 12 weeks has no apparent clinical benefit for dry eye in primary sjogren syndrome. The limitation of our study is a sample size, short course of treatment.

5. Conclusion

According to our study, Retinyl palmitate 0.05% QID daily along with preservative free artificial tears brought about an improvement in Schirmer test, tear film break up time and ODSI score as compared to hydroxychloroquine 400mg daily. Retinyl palmitate has potential to be used in treatment of dry eye disease as there is significant improvement

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