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ORIGINAL ARTICLE

Oral Vitamin A- Including Antioxidant Formula versus Topical Vitamin A Added to Lubricant Eye Drops in Treatment of Dry Eye Syndrome; A Comparative Study

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ABSTRACT

AIM: Is to explore the safety and compare the efficacy of oral (systemic) vitamin A antioxidant with topical vitamin A (eye drops) in treatment of dry eye syndrome and the lasting period of their effects after cessation of therapies.

PATIENTS AND METHODS: This prospective, interventional, randomized, comparative study has been conducted on 160 eyes of 80 patients (aging from 19 to 65 years) divided randomly into two groups; group A included 40 patients; 80 eyes (24 males and 16 females) who received eye drops containing lubricant and topical vitamin A, this eye drop was given to these patients as one drop in each eye every 4 hours during the waking hours for 6 months. While group B included 40 patients; 80 eyes (29 males and 11 females) who received topical lubricant eye drops used as one drop in each eye every 4 hours during the waking hours, and oral vitamin A in the form of capsule given once daily at a fixed time for 6 months. Each capsule contains provitamin A (beta-carotene) and other antioxidant formula.

RESULTS: Symptoms of dry eye syndrome; the most notable changes were seen in blurred vision. At baseline, the mean score for blurred vision in the different treatment groups ranged between 1.09 and 1.35 (on a scale from 0 to 4), with no statistically significant difference among the two groups. The decrease from baseline in blurred vision was statistically significant in the oral vitamin A group at month 2 (from1.35 to 0.9) and month 3 (from 1.35 to 0.53, $p < 0.05$) and in the topical vitamin A group at month 3 (from 1.21 to 1.00, $p < 0.05$). At month 3, the changes from baseline in blurred vision in the two groups were statistically significant but they were significantly different in the oral group from that in the topical group ($p < 0.05$). Statistically significant decreases in photophobia were observed in all treatment groups at month 3 ($p < 0.05$). According to dry eye patient questionnaire, Shirmer's test, and tear break-up time, both treatments relieved dry eye symptoms, but it was earlier, better, and lasting longer in group of oral vitamin A antioxidant.

CONCLUSION: Oral vitamin A antioxidant was more effective and has a lasting effect much longer than topical one. So, it becomes recommended to consider oral vitamin A antioxidant with lubricant eye drops in treatment of dry eye syndrome to relieve symptoms and correct the underlying pathologies including the ocular surface and lacrimal gland.

Key words: Dry eye syndrome; Kertaoconjunctivitis sicca; Corneal vital staining; Antioxidant; Oral vitamin A; Vitamin A eye drops

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INTRODUCTION

Dry eye syndrome (DES), also known as keratoconjunctivitis sicca (KCS), is the condition of having dry eye. Other associated symptoms include irritation, redness, discharge, and easily fatigued eyes. Blurred vision may also occur. The symptoms can range from mild and occasional to severe and continuous. Scarring of the cornea may occur in some cases without treatment[1]. Dry eye occurs when either the eye does not produce enough tears or when the tears evaporate too quickly Dry eye syndrome is a common form of ocular surface disease (OSD) and may overlap with other causes of OSD, such as ocular allergy and meibomian gland dysfunction (MGD)[1].

The ocular surface is an integrated anatomical unit consisting of 7 key interactive and interdependent components: the tear film, the lacrimal and accessory lacrimal apparatus, the nasolacrimal drainage system, the eyelids, the bulbar and tarsal conjunctiva, cranial nerve V, and cranial nerve VII. Abnormalities or deficiencies in any of the 7 ocular surface components may worsen dry eye syndrome, yet promise opportunities for effective therapeutic intervention[2].

Dry eye syndrome may be subdivided into 2 main types; one is associated with Sjogren's syndrome (SS), while the other is unassociated with SS (non-SS KCS).

Dry eye syndrome can also be subdivided into pure aqueous deficiency dry eye and evaporative dry eye [3]. Eighty-six percent of patients with dry eye syndrome also have signs of Meibomian gland dysfunction.

Dry eye syndrome is incredibly common, especially with advancing age and it is more in older women. Recent studies show that dry eye syndrome is on the rise all around the world especially as more and more adults use computers, wear contact lenses, and undergo vision-correcting LASIK or cataract surgery [2].

Insufficient tears cause damage to the interpalpebral ocular surface and are associated with symptoms of discomfort.

The International Dry Eye Workshop (2007) 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].

DES is associated with decreased ability to perform certain activities such as reading, driving, and computer related work, which require visual attention. Patients experience dry eyes symptoms constantly and severely, affecting their quality of life[4].

While no single biological cause of dry eye syndrome is yet known, we do know that chemical stresses and those induced by the high ultraviolet light exposure of the eye are at least in part to blame[5].

But regardless of the trigger, dry eyes ultimately result from a simple imbalance: too little production of tears, or too rapid evaporation of tears on the surface of the eye[6].

In fact, according to a recent estimate, Americans spend about a third of a billion dollars on over-the-counter eye drops, or "artificial tears," each year[7]. That's a substantial investment in a product that produces only short-term relief but that has no long-lasting effect[8].

Eye drops are the most recommended solution mainstream medicine offers for dry eye syndrome. This is problematic for multiple reasons. For starters, commercial, synthetic eye drops are often loaded with chemicals which may cause stinging and other unpleasant side effects[9]. They often require frequent re-application in order to provide any relief at all. But that's the least of their problems.

Vitamin A is known to regulate the proliferation and differentiation of corneal epithelial cells, preserves conjunctival goblet cells, and has been used in the treatment of eye diseases such as dry eye and superior limbic keratoconjunctivitis for some time[10].

Vitamin A is an essential nutrient present naturally in tear film of healthy eyes. Vitamin A plays an important role in production of the mucin layer, the most innermost lubricating layer of tear film that is crucial for a healthy tear film. Vitamin A deficiency leads to loss of mucin layer and goblet cell atrophy[11]. Vitamin A drops protect the eyes from free radicals, toxins, allergens, and inflammation. Topical retinoic acid therapy in conjunction with systemic administration of vitamin A has been investigated to treat xerophthalmia[12]. Effective amount of one or more retinoids alone may be dispersed in a pharmaceutically acceptable ophthalmic vehicle and topically applied for effective treatment of dry eye disorders.

Tseng *et al*[13] demonstrated that topical all-trans retinoic acid ointment was effective in the treatment of four severe cases of the following ocular surface diseases: keratoconjunctivitis sicca, Stevens-Johnson syndrome, drug-induced pseu-dopemphigoid, and surgery-induced dry eye.

In addition to synthetic Vitamin A supplements, we need to know that vitamin A can be obtained from different kind of food, and it is obtained in two different forms: it can be found pre-formed in animal sources – it is also called retinol or retinal; pro-vitamin A – also called beta carotene – is derived from plant sources.

Vitamin A also have been shown effective for the treatment of the following eye diseases: superior limbic keratoconjunctivitis, age-related macular degeneration (AMD), retinitis pigmentosa (RP), loss of peripheral vision, Stargardt's disease[14].

Deficiency of Vitamin A has been shown to contribute to dry eyes. Mild vitamin A deficiency may result in changes in the conjunctiva (corner of the eye) called Bitot's spots. Severe or prolonged vitamin A deficiency causes a condition called xerophthalmia (dry eye), characterized by changes in the cells of the cornea The first line of treatment to insure an adequate level of Vitamin A is a healthy diet with fresh dark green leafy vegetables[15].

The present study assessed whether oral supplement of -vitamin A including- antioxidant formula could improve symptoms and clinical parameters of disease activity and of note, ultra-structural changes in patients with DES.

PATIENTS AND METHODS

A prospective, interventional, randomized, comparative study was conducted on a total number of 80 patients visiting my clinic, within the period of March 2015 and January 2016. The institutional (Al Azhar University) review boards and the local ethics committee approved the trial. A written informed consent was obtained from all patients based on Helsinki protocol.

Inclusion criteria were age of 19 years or more with symptoms of dry eye; fluorescein tear film break-up time (TBUT) less than 10 seconds, Schirmer test less than 10 mm moisture, and, the presence of lid margin scaling, telangiectasia, and meibomian gland plugging on slit-lamp examination.

Exclusion criteria were any pre-existing ocular disease other than DES, history of herpetic eye disease, patients on oral tetracycline or corticosteroids, and corneal surgeries like corneal cross linking, or laser *in situ* keratomileusis (LASIK). Other exclusion criteria included pregnancy, or lactating mothers. The total duration of this study was 9 months; 6 months, in which, patients recieve treatment, and 3 months more, after cessation of treatment with continued follow up to assess the lasting effect period expected after cessation

of treatment with each group.

This study has been conducted on 80 patients (aging from 19 to 65 years) divided randomly into two groups; group A and B.

Group A: 40 patients; 80 eyes (24 males and 16 females) receiving eye drops containing lubricant and topical vitamin A, with the following composition: (Cornetears ED, Orchidia pharma) each gm contains Vitamin A palmitate 10 mg (1000 IU), preserved with Cetremide 0.1 mg & (Carbomer 974, Vitamin E, Tromethamin, Cremophor, Glycerol, Disodium edentate & water). This eye drop was given to these patients as one drop in each eye every 4 hours during the waking hours for 6 months.

Group B: 40 patients; 80 eyes (29 males and 11 females) receiving topical lubricant eye drops containing carboxymethylcellulose, this eye drop was given to these patients as one drop in each eye every 4 hours during the waking hours, and oral vitamin A in the form of capsule given once daily at fixed time for 6 months. Each capsule contains provitamin A (beta-carotene) and other antioxidant formula (OCTATRON, NERHADOU), (Table 1).

The diagnosis of dry eye and evaluation of the treatment outcome for both groups are done using the above measures had been mentioned in inclusion criteria.

These patients were seen at baseline and at months 1, 3, 6 and 9. The total duration is 9 months including 6 months of therapy and 3 months after cessation of it, evaluating the lasting effect of both types of treatments on ocular surface moisture.

The primary outcome measures (3 months after intervention) were the change in subjective symptoms of dry eye according to the score index of ocular surface disease questionnaire (OSDQ) as shown after.

The secondary outcome measures (6 months after intervention) were the scores of Schirmer's test for tear production, TBUT, and fluorescein staining of ocular surface, as a measure of ocular surface integrity and corneal surface integrity for cellular changes and goblet cell well-function after this period of treatment compared with its baseline status. I preferred to delay that measures after this time to detect changes at its peak.

The tertiary outcome measures (9 months after intervention, 3 months after drug stoppage) were score index of OSDQ, Schirmer test, and TBUT.

I have divided the period of follow up in to 3 stages to determine the expected time for each treatment to get impact on DES symptoms and signs, to guide us informing patients about the time needed for treatments to judge if they are effective or not. Aslo, to know about the lasting effect for each.

At each visit, each subject underwent a detailed ocular examination. This included measurement of best corrected visual acuity (BCVA) and slit lamp biomicroscopy. Slit lamp examination included assessment of the lid margins, eye lashes and meibomian gland orifices for any blockage or stenosis. A questionnaire of dry eye symptoms was provided at every visit and scores assigned for each symptom.

Ocular surface disease questionnaire (OSDQ): all patients were asked the following 12 questions, and circle the number in the box that best represents each answer (Tables 2, 3 and 4). Then, fill in boxes A, B, C, and D according to the instructions beside each. It is adapted after Schiffman and Jacobsen [15].

Evaluation of the OSDQ Score is performed by adding subtotals A, B, and C to obtain D (D = sum of answers of the 12 questions), Then, OSDQ score is assessed on a scale of 0 to 100, with higher scores representing greater disability. The score demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. OSDQ is a valid and reliable instrument to measure dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function [16].

Vital staining of ocular surface with fluorescein dye stain (FS), in the form of eye drops or strips, helps the diagnosis of dry eyes and requires examination of the ocular surface using the biomicroscope (slit lamp) with cobalt blue illumination, which provides magnified image of the tear film and the ocular surface status. Fluorescein also allows detection of small areas on the cornea (Punctate corneal epithelial erosions) where the lining cells have been lost due to dryness or other forms of damage [17].

To avoid the mild irritation which may occur with fluorescein dyes, I used to use Benoxinate eye drops for ocular surface anesthesia prior to ocular staining to get an accurate measurement.

Schirmer test is performed by placing the end of a special paper strip inside the lower eyelid of each eye. Both eyes were tested at the same time. Before the test, numbing eye drops were given to prevent your eyes from tearing due to irritation from the paper strips.

Normal Results: More than 10 mm of moisture on the filter paper after 5 minutes is a sign of normal tear production. Both eyes normally release the same amount of tears. Less than 10 mm of moisture of filter paper can diagnose dry eye, and the lesser the scale number the severer the condition [18].

Tear break up time (TBUT) was done as follows: fluorescein is instilled into the patient's tear film and the patient was asked not to blink while the tear film was observed under a broad beam of cobalt blue illumination. The TBUT is recorded as the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film, as seen in this progression of these slit lamps photos over time. A TBUT under 10 seconds is considered abnormal[19].

RESULTS AND STATISTICS

There were no statistically significant differences in age, gender, or pretreatment tear film or ocular surface parameters among the two patient groups. A total of 80 patients were enrolled in equal numbers across the two treatment groups. The first patient was enrolled in March 2015, and the last patient completed the nine-month treatment and evaluation in January 2016.

Symptoms of dry eye syndrome; the most notable changes were seen in blurred vision. At baseline, the mean score for blurred vision in the different treatment groups ranged between 1.09 and 1.35 (on a scale from 0 to 4), with no statistically significant difference among the two groups. The decrease from baseline in blurred vision was statistically significant in the oral vitamin A group at month 2 (from1.35 to 0.9) and month 3 (from 1.35 to 0.53, $p < 0.05$) and in the topical vitamin A group at month 3 (from 1.21 to 1.00, $p < 0.05$). At month 3, the changes from baseline in blurred vision in the two groups were statistically significant but they were significantly different in the oral group from that in the topical group ($p < 0.05$). Statistically significant decreases in photophobia were observed in all treatment groups at month 3 ($p < 0.05$).

Statistically significant improvements in irritation also were observed in both the oral and topical vitamin A groups in all follow-up periods ($p < 0.05$). But the topical vitamin A group experienced irritation on dripping the vitamin A eye drops during the first month of therapy. These improvements in dry eye symptoms, according to OSDQ scores, were more apparent in the oral vitamin A group but both groups took the same time for the patients to feel. Schirmer test and TBUT test results: At baseline, the mean TBUT in the both treatment groups ranged between 3.43 and 3.57 seconds, with no statistically significant differences between the groups.

At month 2, there was a statistically significant improvement in tear film BUT in both the topical vitamin A group (from 3.75 - 1.92 seconds to 5.93 - 2.02 seconds) and the oral vitamin A group (from 3.57 - 1.56 seconds to 6.25 - 3.19 seconds; $p < 0.05$). At months 3 (Figure 1) and 4, the changes from baseline in TBUT in the oral vitamin A groups were significantly different from that in the topical vitamin A group ($p < 0.05$).

However, there was significant difference in the improvement of the TBUT between the topical and oral vitamin A groups in the late follow-up periods (Figure 2).

At baseline, the mean Schirmer values in the two treatment groups ranged between 3.97 and 3.63 mm, with no statistically significant differences between the groups (Figure 3). At month 4, there was a statistically significant improvement in Schirmer values in the oral vitamin A group ($p < 0.05$).

The outcomes of tear function tests (Schirmer's, TBUT, and FS) on day 1 and at completion (day 180), were compared. Chi-square test was used to establish the strength of association (Table 5). They had a statistically significant relation at the 1% level ($p < 0.001$) for the oral group and a statistically insignificant relation at the 1% level ($p = 0.564$) for the topical group.

Evaluation of symptoms (Table 7) and tear tests, 3 months after stoppage of treatments in both groups by assessing symptoms of dry eye syndrome according to the mean score of OSDQ and results of tear tests (Schirmer and TBUT) At the end of 9 months (Figure 4) (Tables 6, 8 and 9) showed statistically significant difference between the two groups. In the oral vitamin A group at month 9 the results were like that at month 6 indicating lasting effect, while in the topical Vitamin A group at month 9 were like that at month 1, with regressing effect, not lasting as in oral group.

The results in the two groups were statistically significant but they were significantly different in the oral group from that in the topical group ($p < 0.05$).

Also, some patients of the topical group experienced a temporary burning sensation lasting about 10 minutes after dripping the vitamin A eye drops within the first month of treatment, this sensation was not present with the oral group who were using lubricant eye drops, so it is suggested that burning sensation is due to vitamin A palmitate more than the preservative substance.

Statistical analysis was performed with Pearson Chi-square test. Means between groups were compared using the *t*-test. *P* values were calculated at 1% and 5% confidence interval for Chi-square tests and 95% confidence interval for the *t*-test respectively. A *P* value of less than 0.001 at 1% and 95% confidence interval was statistically significant.

DISCUSSION

Dry eye syndrome is a very common ocular surface disease that is caused by either abnormal tear production or abnormal ocular surface anatomical or cellular components.

Vitamin A either oral or topical is considered as an effective treatment for DES, leading to significant improvement in symptoms and quality of life. This represents a noteworthy improvement over commercial lubricant eye drops, which contain ingredients that some people are allergic to and only provide temporary relief[20].

This unique oral approach is capable of relieving dry eyes by supporting natural tear production and enhancing the ocular surface integrity and smoothening, that means you can take a single capsule once daily and experience soothing, youthful tear production day in and day out. Patients with dry eye symptoms have found lasting improvement in eye comfort.

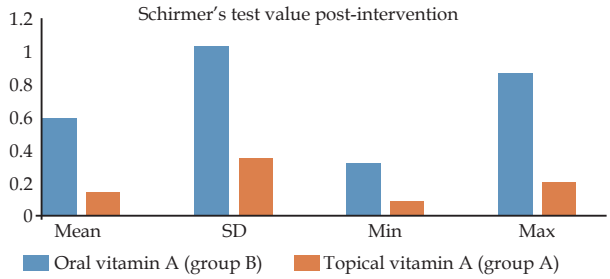

Figure 1 Graph showing schirmer's test value in both groups 3 months after onset of treatment.

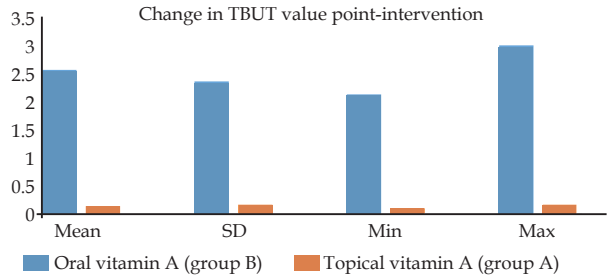

Figure 2 Graph showing TBUT value in both groups 3 months after onset of treatment.

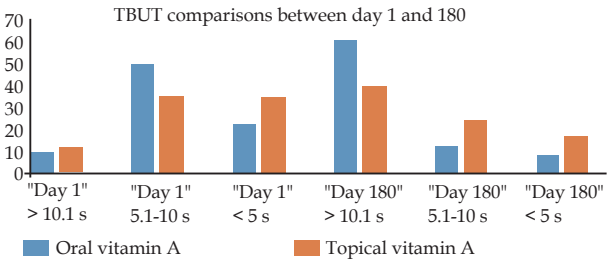

Figure 3 Graph comparing TBUT values on day1 and day 180 from onset of treatment.

Table 1 Components of the oral capsule.

Each capsule contains	
Zinc (amino acid chelated); Esssntial for Metallothionine enzyme.	11 mg
Selenium (amino acid chelated); Component of Glutathione peroxidase enzyme.	55 mcg
Molybdenum (amino acid chelated); A transfer agent in redox reactions.	45 mcg
Mixed Bioflavonoids; Antioxidant activity, synergistic effect.	100 mg
Biotin (Natural Vitamin B7); Synergistic effect, essential for metabolism.	10 mcg
Vitamin E (Natural α-tocopherol); Essential antioxidant, protects cell membrane.	15 IU
Vitamin A (Natural Beta carotene); Vitamin A precursor, important antioxidant.	3000 IU
Vitamin C (Natural ascorpic acid); powerful water solubable antioxidant vitamin.	90 mg

Table 2 OSDQ part 1.

Have you experienced any of the following during the last week?	All of the ime	Most of the time	Half of the time	Some of the time	None of the time
Eyes are sensitive to light?	4	3	2	1	0
Eyes feel gritty?	4	3	2	1	0
Painful or sore eyes?	4	3	2	1	0
Blurred vision?	4	3	2	1	0
Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 = A.

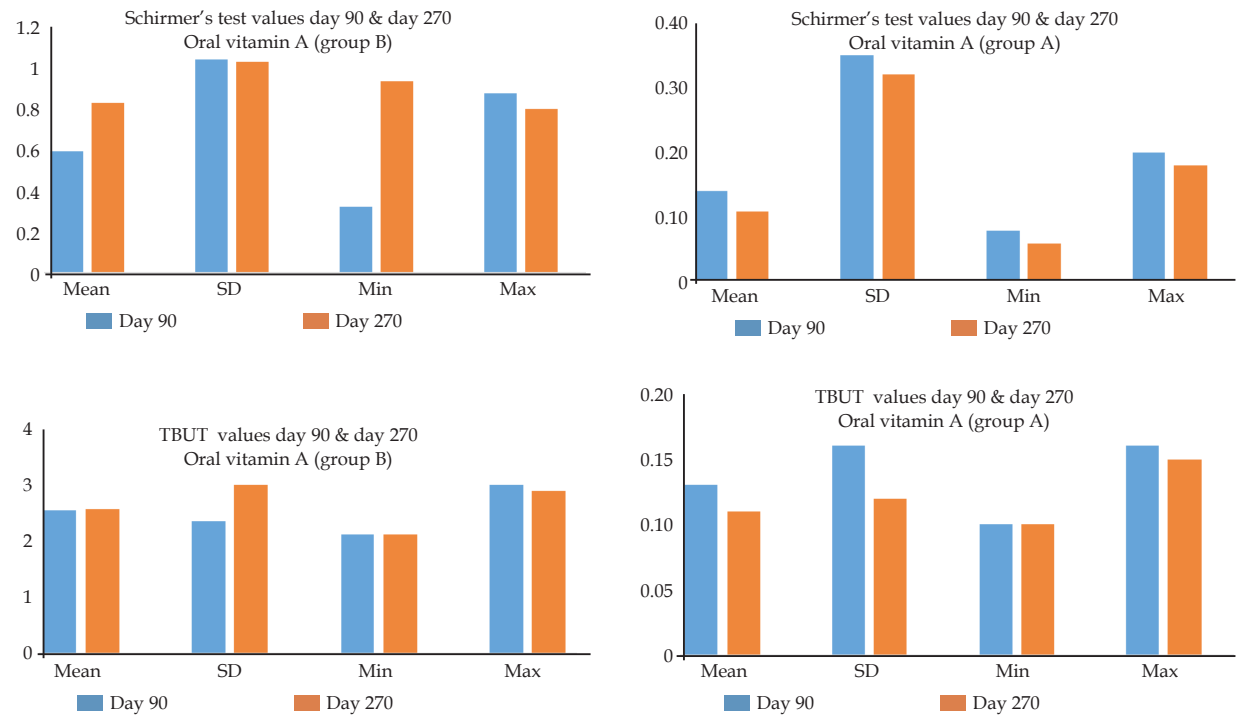

Figure 4 Upper right and left; graphs showing schirmer's test values in both groups 3 months after stoppage of treatment. Lower right and left; graphs showing TBUT values in both groups 3 months after stoppage of treatment

Table 3 OSDQ part 2.

Have problems with your eyes limited you in performing any of the following during last week?	All of the time	Most of the time	Half of the ime	Some of the time	None of the time
Reading?	4	3	2	1	0
Driving at night?	4	3	2	1	0
Working with computer	4	3	2	1	0
Blurred vision?	4	3	2	1	0
Watching TV	4	3	2	1	0

Subtotal score for answers 6 to 9 = B.

Table 4 OSDQ part 3.

Have your eyes felt uncomfortable in any of the following situations during the last week?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
Windy conditions?	4	3	2	1	0
Places with low humidity?	4	3	2	1	0
Areas that are air conditioned?	4	3	2	1	0

Subtotal score for answers 10 to 12 = C.

Table 5 Changes in Schirmer's values (secondary outcome).

Change in Schirmer's value	N	Mean	SD	Min	Max	*t*-test
Oral vitamin A (group B)	80	0.59	1.03	0.32	0.87	
Topical vitamin A (group A)	80	0.14	0.35	0.08	0.2	
Total	160	0.38	0.82	0.27	0.49	0.00

Table 6 Change in TBUT values post-intervention (secondary outcome).

Change in TBUT values	N	Mean	SD	Min	Max	*t*-test
Oral vitamin A (group B)	80	2.54	2.34	2.11	2.98	
Topical vitamin A (group A)	80	0.13	0.16	0.1	0.16	
Total	160	1.33	2.05	1.07	1.60	0.000

Table 7 Tear film break up time comparisons.

Group	TBUT day 1			TBUT day 180			total
	> 10.1 s	5-10 s	< 5s	> 10.1 s	5-10 s	< 5s	
Oral vitamin A	9	49	22	60	12	8	80
NO. & % of pts. group B	11.3%	61.3%	27.5%	75%	15%	10.0%	100%
Topical vitamin A	11	35	34	39	24	17	80
NO. & % of pts. group A	13.8%	43.8%	42.5%	48.8%	30%	21.3%	100%

Table 8 Change in symptoms score post-drug stoppage (tertiary outcome).

Change in symptoms score	N	Mean	SD	Min	Max	*t*-test
Oral vitamin A (group B)	80	2.01	0.76	1.28	2.49	
Topical vitamin A (group A)	80	0.18	0.12	0.26	0.51	
Total	160	1.91	0.51	0.85	1.51	0.000

Table 9 Change in Schirmer's test values post-drug stoppage (tertiary outcome).

Change in Schirmer's value	N	Mean	SD	Min	Max	*t*-test
Oral vitamin A (group B)	80	0.82	1.02	0.93	0.79	
Topical vitamin A (group A)	80	0.11	0.32	0.06	0.18	
Total	160	0.32	0.72	0.25	0.47	0.000

Table 10 Change in TBUT values post-drug stoppage (tertiary outcome).

Change in TBUT value	N	Mean	SD	Min	Max	*t*-test
Oral vitamin A (group B)	80	2.56	2.98	2.11	2.88	
Topical vitamin A (group A)	80	0.11	0.12	0.10	0.15	
Total	160	1.29	2.02	1.07	1.40	0.000

This treatment has been found to address the cause of dry eyes with research proving its use leads to long-lasting improvement in eye comfort[21].

It was difficult to imagine an oral treatment having such a profound impact on tear production and correction of ocular surface errors. This is because mainstream medicine's preferred treatments for dry eye syndrome are in the form of eye drops, both over-the-counter and prescription.

A study done by the Division of Ophthalmology at Kansai Rosai Hospital in Hyogo, Japan treated 12 patients with topical Vitamin A eye drops to treat superior limbic keratoconjunctivitis patients for three months with outstanding results – 10 patients or 83% saw no recurrence. Other studies have found that preservative-free Vitamin A drops can help substantially in treating dry eye symptoms, some even better than more expensive prescription drops[22].

Some eye drops contain a vasoconstrictor in order to help with the discomfort of dry eyes. The main ingredient in such drops is usually tetrahydrozoline. While it has been shown to improve the redness associated with dry eyes after a single use, its effectiveness diminishes over a 10-day period, potentially encouraging overuse of the product[23].

People who suffer from dry eye syndrome know that its symptoms include burning, eye fatigue, sensitivity to light, blurred vision, and stringy mucous can have a significant impact of their quality of life. With this in mind, Japanese researchers wanted to determine if also topical vitamin A formula could positively impact quality of life and eye comfort in addition to increasing tear production.

They found it can do both, through a study done by the Division of Ophthalmology at Kansai Rosai Hospital in Hyogo, Japan, treated 20 patients with topical Vitamin A eye drops to treat keratoconjunctivitis sicca for three months with outstanding results. 17 patients or 81% showed good results including improvement of symptoms and signs of dry eye disease. Other studies have found that preservative-free Vitamin A drops can help substantially in treating superior limbic keratoconjunctivitis, some even better than more expensive prescription drops[24].

These same patients also completed a "dry eye-related quality of life score" test (DEQS), designed to measure the impact of bothersome eye symptoms themselves, as well as their impact on daily life. The lower the score the better the ocular surface, with a maximum total score of 60.

Both dosing groups had a total composite score (eye and daily life symptoms) of about 40 at the beginning of the study. Once treatment began, the scores fell in both groups, but was more rapid in oral group. This supports the longer-lasting effects of the long-term use of oral formula seen on symptoms and on the test of tear production as well.

The vitamin A eye drops used in our study are preserved and their Composition was shown above. While the systemic vitamin A-including antioxidant formula was given as a soft oral capsules taken once daily, one hour after meal, and the capsule composition was also shown above. Vitamin A is known to regulate the proliferation and differentiation of corneal epithelial cells, preserves conjunctival goblet cells, and has been used in the treatment of eye diseases such as dry eye and superior limbic keratoconjunctivitis for some time[25].

Tseng *et al*[26] demonstrated that topical all-trans retinoic acid ointment was effective in the treatment of four severe cases of the following ocular surface diseases: keratoconjunctivitis sicca, Stevens-Johnson syndrome, drug-induced pseu-dopemphigoid, and surgery-induced dry eye. Impression cytologic analysis, dry eye symptoms, visual acuity, keratopathy, and the Schirmer test results all improved after the use of topical all-trans retinoic acid ointment. Polysorbate 80 is used as a surfactant and demulcent, but it is an oxygen radical scavenger and a likely antioxidant, similar to carotene.

Topical cyclosporine A 0.05% also has been shown to be effective in the treatment of moderate to severe chronic dry eye in a masked, multicenter, phase III clinical trial.5 Several mechanisms for the action of cyclosporine emulsion have been identified, including the inhibition of epithelial apoptosis and of cytokine production by the activated T lymphocytes that infiltrate the conjunctiva in keratoconjunctivitis sicca. The action of cyclosporine is thought to occur through its effects on subconjunctival and lacrimal gland inflammation.

These treatments cause an increase in tear production and conjunctival goblet cell densities in a significant number of patients with moderate to severe chronic dry eye who receive treatment[27].

In the present study, we investigated the efficacy of oral vitamin A antioxidant formula and topical A eye drops in the treatment of dry eye syndrome and compared the long lasting therapeutic effects of the two agents. Both oral and topical vitamin A treatments improved symptom scores, tear film BUT, corneal staining scores, a decrease in stingy mucus secretion, and improvement of conjunctival health.

In this study, the corneal staining score improved faster in the oral vitamin A group than in the topical vitamin A group. Therefore, oral vitamin A may be a more effective treatment for the ocular surface disintegrity caused by dry eye in the relatively early treatment period. The two lines of treatment may improve subjective symptoms. In this study, blurred vision was significantly improved in the oral vitamin A group from month 2 and in the topical group from month 4 ($p < 0.05$). Hypothesize that blurred vision improved in the oral vitamin A group faster than in the topical vitamin A group because the Schirmer score increased in the oral group earlier than in topical one.

Dry eye syndrome is common, especially in older adults. Its effects can impact your mental and physical well-being. The underlying issues involved in dry eye syndrome are simple: too little watery tear production in the lacrimal glands means not enough water gets into your tears to fully moisten the eye surface, while too little oil production in the Meibomian glands means too much water evaporates from the eye surface, again leaving it exposed to damage[28].

These forces can change the very composition of your tears, leaving them over concentrated and incapable of properly lubricating the surface of your eyes. Now a natural, orally-administered nutrient can soothe your eyes from the inside out by stimulating healthy tear production to restore your eye's delicate ecosystem[29].

Other researchers studied the effect of oral omega-3 for treatment of dry eye, they had shown a very satisfying results in their study, almost similar to our results especially if dry eye syndrome is related to oil layer deficiency[30].

Finally, from the results of this study, it becomes clear that both topical and systemic vitamin A has a role in treatment of dry eye syndrome, but it was more valuable with the oral vitamin A than topical one. Oral vitamin A antioxidant was more effective and has a lasting effect much longer than topical one. So, it becomes recommended to consider oral vitamin A antioxidant with lubricant eye drops in treatment of dry eye syndrome to relieve symptoms and correct the underlying pathologies including the ocular surface and lacrimal gland.

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