European Journal of Ophthalmology / Vol. 19 no. 3, 2009 / pp. 337-342

Antioxidants intake and dry eye syndrome: a crossover, placebo-controlled, randomized trial

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PURPOSE. *To assess whether an orally administered antioxidant dietary supplement could improve the objective clinical signs and alleviate the subjective symptoms of dry eye syndrome.*
METHODS. *Twenty-four subjects diagnosed with dry eye syndrome were randomized in a crossover, double-blind, controlled, randomized study to receive a placebo or an antioxidants combination (Oxybiane®) for 12 weeks. In all subjects, break-up time (BUT) test, Schirmer test, ocular symptoms (sore eyes, burning, itching, sensation of foreign object in the eye, photophobia, sticky eyes, and redness), visual comfort, and general well-being were evaluated weekly.*
RESULTS. *After 12 weeks of supplementation with Oxybiane®, both the BUT scores (27.3%±8.4% with Oxybiane® versus 3.61%±4.3% with the placebo, p=0.017) and the Schirmer scores (26.9%±14.2% with Oxybiane® versus –4.7%±3.4% with the placebo, p=0.037) were significantly increased. A significantly improvement was also observed considering subjective clinical symptoms such as burning (p=0.031), itching (p=0.027), sensation of foreign body in eye (p=0.030), and redness (p=0.043).*
CONCLUSIONS. *Supplementation with oral antioxidants can improve both tear stability and quantity but also subjective clinical signs. (Eur J Ophthalmol 2009; 19: 337-42)*

KEY WORDS. *Antioxidants, Dry eye, Tear stability, Tear volume*

Accepted: September 12, 2008

INTRODUCTION

The fluids and tissues of the eye are uniquely exposed to light, and this produces reactive oxygen species (1). Oxidative damage to protein, lipid, and DNA is thought to play a key role in the development of ocular disorders including cataracts (2), age-related maculopathy (3), and dry eye syndrome (4). The ocular surface is in fact relatively unprotected and consistently exposed to radiation, atmospheric oxygen, environmental chemicals, and physical insults, resulting in the generation of reactive oxygen species, which are thought to contribute to ocular damage. Both oxidative tissue damage and polymorphonuclear leucocytes indicating an oxidative potential occur in the tear film of patients with dry eyes (4). These reactions lead to severe damage of the involved tissue. Free radicals and inflammation may be involved in the pathogenesis or in the self-propagation of the disease.

Dry eye syndrome is a significant public health problem affecting 10% of the adult population and 18% of the elderly population. Dry eye is a condition produced by the inadequate interrelation between lachrymal film and ocular surface epithelium, and is caused by quantitative and qualitative deficits in one or both of them (5). It can be

 1120-6721/337-06$25.00/0

produced by one or combined etiologic causes, affecting one or several of the secretions of the glands serving the ocular surface, and producing secondary manifestations of different grades of severity. Symptoms of ocular discomfort can be debilitating and, when severe, may affect psychological health and ability to work. These symptoms range from mild transient irritation to persistent dryness, burning, itchiness, redness, pain, ocular fatigue, and visual disturbance. Despite progress in determining the etiology and pathogenesis of dry eye syndrome, current knowledge remains inadequate, and no preventive strategies have been found. Moreover, the most common therapy for dry eye syndrome, artificial tears, provides only temporary and incomplete symptomatic relief (6). Therefore, identification of modifiable risk factors for dry eye syndrome may suggest avenues for investigation of novel preventive and treatment measures. The purpose of this study was to assess whether an orally administered antioxidant dietary supplement could improve the objective clinical signs and alleviate the subjective symptoms of dry eye syndrome.

METHODS

Subjects

Twenty-four subjects (16 women and 8 men; average age, 55.2 ±11.8 years) diagnosed with dry eye were enrolled in this crossover, double-blind, controlled, randomized study. The recruitment and the diagnostic workup were performed by three French ophthalmologists between January 2001 and November 2001. The study was approved by the "CCPPRB d'Auvergne" Ethics Committee on March 6, 2000. All patients were over 18 years of age and provided consent before being recruited into the study and after receiving a full explanation of all procedures.

Subjects with dry eye were identified on the basis of the typical symptoms of dry eye (sore eyes, burning, itching, sensation of foreign object in the eye, photophobia, sticky eyes, redness), visual acuity corrected ≥ 2/10, break-up time (BUT) scores ≤ 10 seconds, and Schirmer scores ≤ 10 mm/5 minutes (7).

The exclusion criteria were previous ocular infection or inflammation during 3 months before the study, previous ocular surgery or ocular laser therapy during 3 months before the study, punctum plug installation or removal, wearing contact lenses 1 week before the study and during the study, and ocular treatment other than artificial tears 1 month before the study.

Experimental design

After enrollment, the subjects were randomly allocated to receive either two capsules of Oxybiane® or placebo for 12 weeks. After a 4-week washout period, subjects were crossed over to another 12 weeks of capsules. Oxybiane® is a commercially available food supplement containing vitamins C, E, PP, B6, B2, B1, and B9, zinc, β-carotene, lycopene from tomato, polyphenols from grape marc, and *Porphyra umbilicalis* extract (Porphyral HSP®) (Tab. I). The placebo for the study was of identical color, texture, shape, and size; however, it contains only lactose (0.54 g per capsule).

In all subjects, BUT test, Schirmer test, ocular symptoms (sore eyes, burning, itching, sensation of foreign object in the eye, photophobia, sticky eyes, and redness), visual comfort, and general well-being were evaluated.

The BUT test was used to determine the tear stability and to investigate the ability of the tear film to adequately cover the otherwise exposed anterior surface of the eye, for a sufficient duration of time to prevent drying and subsequent damage to the underlying tissues. Both eyes were tested three times and an average value was calculated. The abnormal cutoff value for dry eye diagnosis was a value less than or equal to 10 seconds.

TABLE I - COMPOSITION OF OXYBIANE®

Ingredients	Quantity, mg/capsule
Hydrolyzed wheat proteins	144.6
Acerola powder (25% of vitamin C)	80
Wheat germ powder	50
Zinc sulphate	48.4
Beta-Carotene	42
Vitamin PP	18
Vitamin C	40
Soy natural vitamin E	15.5
Tomato powder	9.3
Porphyra umbilicalis powder (Porphyral HSP®)	5
Grape marc powder	2
Vitamin B6	2
Vitamin B2	1.6
Vitamin B1	1.4
Vitamin B9	0.2

The Schirmer test was used to determine whether the eye produces enough tears to keep it moist. The test is performed by placing filter paper inside the lower lid of the eye. After 5 minutes, the paper was removed and tested for its moisture content. Both eyes were tested at the same time and an average value was calculated. The abnormal cutoff value for dry eye diagnosis was a value less than or equal to 10 mm wetting over 5 minutes.

The seven ocular symptoms (sore eyes, burning, itching, sensation of foreign object in the eye, photophobia, sticky eyes, and redness) were evaluated independently at baseline (week 0) and after 12 weeks of supplementation (week 12) by the ophthalmologists. The absence of the ocular symptom tested was quoted 0 and the presence was quoted between 1 and 3: 1 = tiny, 2 = moderate, 3 = severe.

Visual comfort and general well-being were assessed by the patient using a 100-mm visual analogue scale (0 = perfect; 100 = very bad) between weeks 1 and 12.

Statistical analysis

Week 0 was considered the baseline and week 12 the end of the supplementation. Answers on visual analogue scales were measured in centimeters of the distance separating the point corresponding to the answer given by the subject from the origin of the analogical scale.

In order to compare the results before and after treatment, parametric Student t tests were used for data, which followed normal distribution and distribution free statistical tests for non normal data. A probability level less than 5% was considered statistically significant.

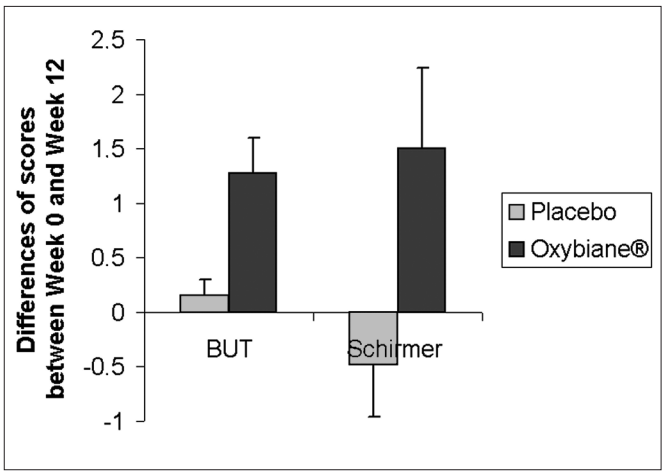

Fig. 1 - *Differences of break-up time and Schirmer scores after 12 weeks of supplementation with Oxybiane® or with the placebo.*

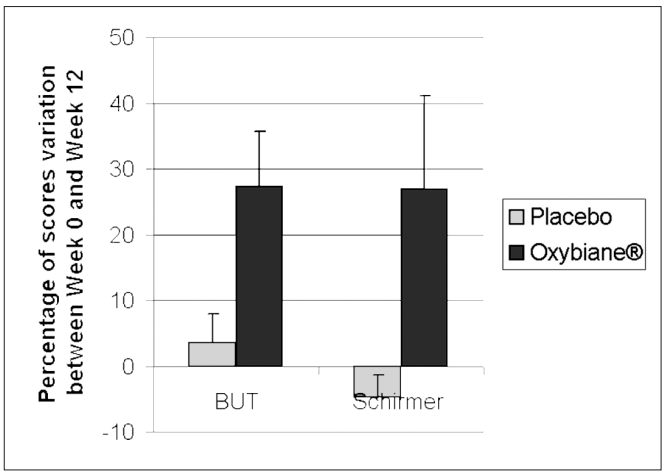

Fig. 2 - *Percentage of break-up time and Schirmer scores variation.*

RESULTS

Objective clinical signs

The BUT scores were found to be increased more significantly during the Oxybiane® supplementation than during placebo, +1.27 seconds (±0.33) versus +0.15 seconds (±0.23) (p=0.007) (Fig. 1). The tears quality was increased by 27.3% (±8.4%) during the Oxybiane® supplementation versus 3.61% (±4.3%) during placebo (p=0.017) (Fig. 2).

The Schirmer scores increased only during the Oxybiane® period, +1.50 mm (±0.74) over 5 minutes versus –0.48 mm (±0.27) during placebo (p=0.016). The tears quantity increased by 26.9% (±14.2%) after 12 weeks of supplementation with Oxybiane® and decreased by 4.7% (±3.4%) after 12 weeks of supplementation with placebo (p=0.037).

Subjective clinical signs

Ocular symptoms. In contrast to the placebo supplemented period, subjects supplemented with Oxybiane® reported a significant improvement between weeks 0 and 12 regarding burning, itching, sensation of foreign object in the eye, and redness (p=0.031, 0.027, 0.030, and 0.043, respectively) (Fig. 3). It represented an improvement of 44.0% for burning, 37.5% for itching, 60.0% for sensa-

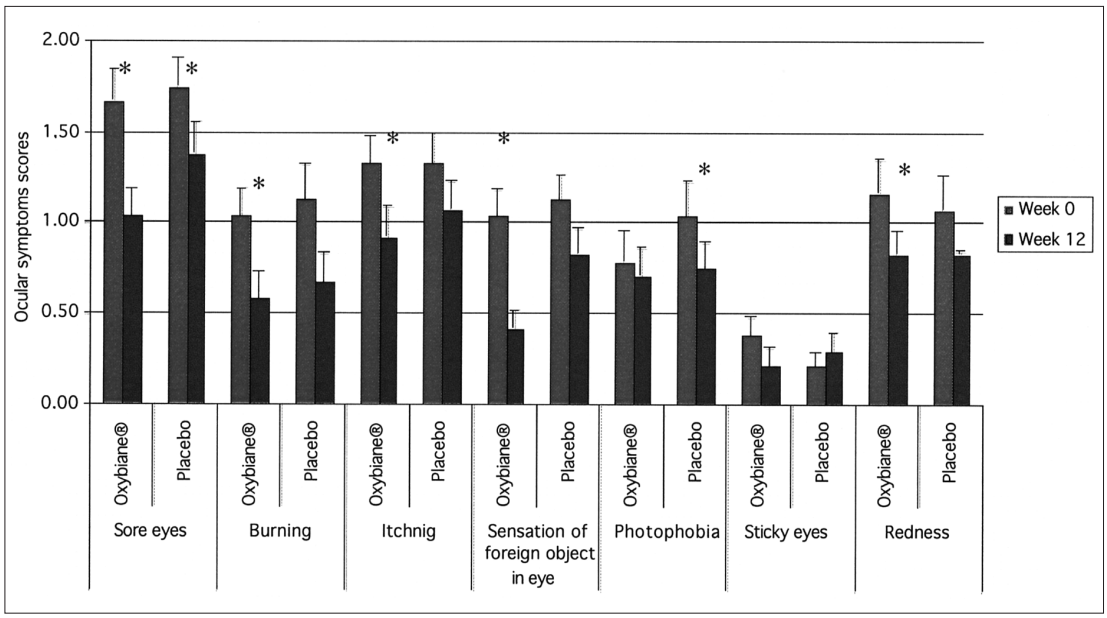

Fig. 3 - *Ocular symptoms scores at week 0 and week 12 (*p<0.05).*

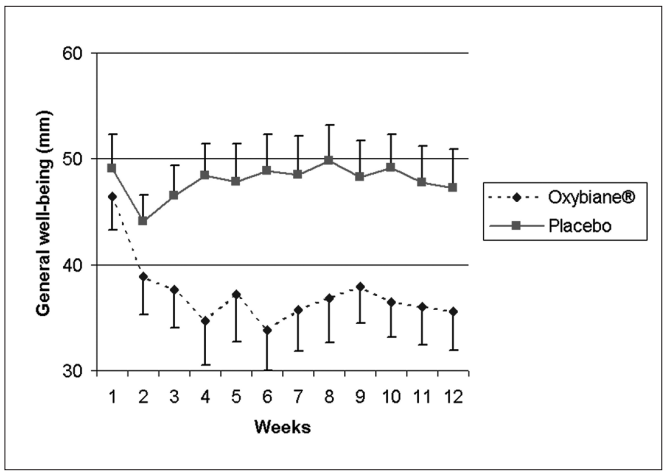

Fig. 4 - *Visual comfort during Oxybiane® and placebo supplementation.*

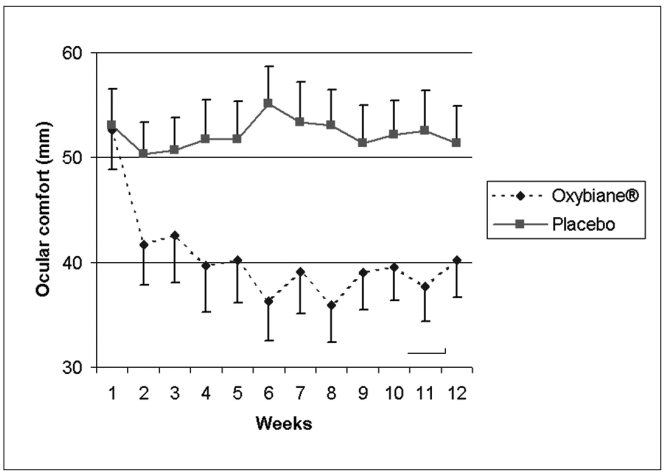

Fig. 5 - *General well-being during Oxybiane® and placebo supplementation.*

tion of foreign object in the eye, and 28.6% for redness.

Sore eyes improved in both supplementation periods, p=0.006 for Oxybiane® and p=0.047 for placebo.

Ocular comfort and general well-being. The average ocular comfort and general well-being were not significantly different at week 1 between both supplementation periods (p=0.576 and p=0.929, respectively). After 12 weeks of supplementation, a significant improvement was observed for the Oxybiane® period: 40.17 mm (±3.51 mm) with Oxybiane® versus 51.38 mm (±3.77 mm) with placebo, p=0.035 considering ocular comfort (Fig. 4); 35.54 mm (±3.63 mm) with Oxybiane® versus 47.21 mm (± 3.67 mm), p=0.028 considering general well-being (Fig. 5).

DISCUSSION

Abnormalities in the production, quality, or replenishment of the tear film will result in various pathologic states regarded as dry eye conditions (8). Such conditions can result in ocular surface damage, and may

lead to eventual corneal damage which could impair corneal transparency and visual performance. The amelioration of symptoms and ocular surface conditions is an important but difficult goal to achieve in patients with dry eye. The involvement of nutritional components in etiology of some dry eye states has been reported.

A recent study found that women with a higher dietary intake of omega-3 fatty acids have a lower prevalence in women who consumed ≥ 5–6 servings/week compared with women who consumed ≤ 1 serving/week of tuna fish (9). One randomized trial of 28.5 mg linoleic acid plus 15 mg γ-linolenic acid twice a day compared with placebo once reported significant reductions in dry eye symptoms, lissamine green staining, and ocular surface inflammation (10). Patel et al demonstrated a significant increase in tear film stability following supplementary multivitamin (A, B1, B2, B6, E) and trace elements (calcium, iron, manganese) intake by a normal Western population (11). They reported that the synergistic effects of a multivitamin-trace elements treatment were more predictable than the effects of a single nutritional component alone (vitamin C). Peponis et al also showed that vitamin C and E supplementation decreases NO levels in the lavage fluid from the ocular surface of diabetic patients and also improves the tear film stability (12). In the study of Blades et al, oral antioxidants improved both tear stability and conjunctival health but did not promote a net increase in tear volume in marginal dry eye sufferers (13). Our study is the first one to show that a specific supplementation with antioxidants, Oxybiane®, for 12 weeks, significantly improves both quality and quantity of tears and then contributes to improve lachrymal functions. It also reduces ocular discomfort regarding burning, itching, sensation of foreign body in eye, and redness. However, even if the benefits of Oxybiane® are evident, it has not yet been determined if these benefits are due only to increase of the aqueous secretion, or also to improvement of the mucin deficiency, the lipodeficiency, and the epithelium, or all of them.

The nutritional influences on tear film composition and physiology are complex and there are several mechanisms that could explain our findings and the clinical improvement mediated by the antioxidants. The antioxidant properties of vitamins C and E could protect the ocular surface from free radicals attack and preserve the integrity of the surface epithelium. Additionally, vitamins A, C, and E are needed for cell differentiation, development, and maintenance. Vitamin C could have an endogenous anti-inflammatory role in the eye. Ascorbate (vitamin C) is an effective water-soluble antioxidant vitamin and ocular tissues are particularly rich in ascorbate (14). The high ascorbate level protects key ocular sites against oxidative damage. Ascorbate has been reported to be important in promoting corneal wound healing and for tear stability (11, 15). Certain systemic conditions with associated dry eye symptoms also allow other dietary factors to be identified as being important for the health or homeostasis for the tear film (e.g. zinc, vitamin B6, niacin) (16). For example, vitamin A is known to be involved in epithelial differentiation and as such is an important micronutrient, essential for the development of the mucus producing goblet cells of the conjunctiva (17).

In conclusion, the oral administration of antioxidants can represent a valid interest in addition to the medical therapy used in dry eye syndrome and can improve quality and quantity of tears as well as visual comfort.

ACKNOWLEDGEMENTS

This study was sponsored by PiLeJe, Paris, France.

Oxybiane® is a product of PiLeJe. Sophie Drouault-Holowacz, Séverine Bieuvelet, and André Burckel are staff members of PiLeJe. There is no conflict of interest for the other authors.

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