

# Treatment of Periorbital Hyperpigmentation with Topical Vitamin K/Vitamin A

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**D**ark circles under the eyes is a very disconcerting problem. Although products have come on the market that purport to treat this entity, no published study has shown the efficacy of any treatment modality. Part of the difficulty in developing a topical agent to address this clinical entity is the lack of current understanding as to the nature of the condition and the various factors that lead to its expression.

Periorbital and suborbital pigmentation in actuality can be a combination of a number of different factors. It is certainly apparent that this problem is somewhat inherited, since the darkness is often present in very young individuals. There is also familial or ethnic tendency to an increase in melanin in this area that is manifested as young as teenage years and continues through life. Additionally, in some individuals there is a thinness in the skin of the lower lids, allowing for pigment as well as vessels to be visible through the skin. This particular problem has not been correctable even with surgery up until this time.

Two factors combine to make this condition worse with time: gravity and actinic damage. Gravity affects all aspects of the aging face, but particularly noticeable are those areas that lack either subcutaneous substance or surrounding support. This is particularly true of the periorbital area! The skin of the area moves downward, stretching and thinning it even more, allowing more blood vessels and the orbicularis muscle to become more obvious, creating an increase in the darkness of the area.

Actinic damage plays a significant role in the aging of skin, probably accounting for approximately 80% of what is called aging.<sup>2</sup> As the skin is exposed to UV, more redness, increased vascularity, broken vessels, dead end vessels and a thinness of the skin occurs.<sup>3</sup> In particular, UVA significantly thins the skin and increases

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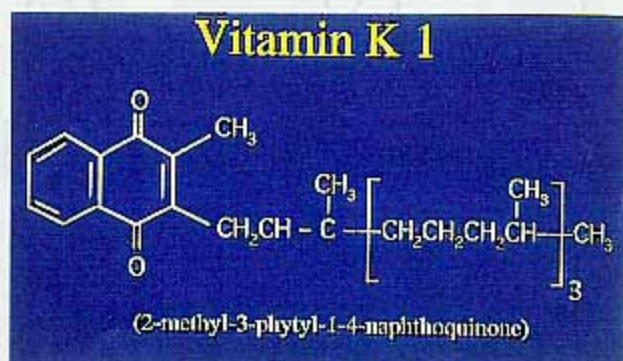


Fig. 1: Structure of phytonadione (Vitamin K<sub>1</sub>).

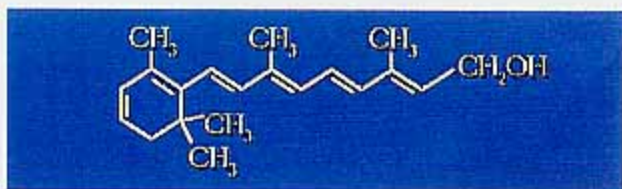


Fig. 2: Structure of retinol.

the background melanin content of the skin.<sup>4</sup> When this occurs in an area in which the skin is already thin, the result can be an increase in the underlying problem, regardless of its nature. Thus, the combination of an inherited tendency to increased melanin in the area, increased vessels and actinic damage of the area can produce the dark circles. No single formulation has been able to address this combination of factors and certainly no moisturizer can affect it in any way.

## THE FORMULATION

A formulation has been developed consisting of vitamin K<sub>1</sub>, (phytonadione) (Fig. 1), and vitamin A (retinol) (Fig. 2) in a Microsponge<sup>®</sup> system (Advanced Polymer Systems, Redwood City, CA). Topical Vitamin K<sub>1</sub> has been shown in another study to decrease the appearance of dark circles.

The formulation used in this study consists primarily of 1% Phytonadione and 0.15% retinol entrapped in a





Fig. 3a: 47-year-old white female at baseline.



Fig. 3b: Same patient, 16 weeks later.

polymeric delivery system. The effects of retinoids (vitamin A derivatives) are well known on both the dermis and the epidermis. In the treatment of photoaging, there is normalization of epidermal turnover leading to a more compact stratum corneum, re-establishment of the rete ridges and improvement of the full epidermal architecture. In addition, there is repair and increase in dermal vessels to a small degree.<sup>6</sup> Vitamin K has been shown in clinical studies to prevent and erase purpura, decrease pigment, and repair blood vessels in the skin.<sup>7</sup> Due to the similarities between its chemical structure and that of ubiquinone, it seems reasonable to assume that vitamin K<sub>1</sub> can be both an antioxidant and a bleaching agent.

By slowly controlling the release of the vitamins into the skin, the polymeric system reduces the tendency for the retinol to produce irritation, and thus results in a greater overall penetration of the vitamin over time. Also, there appears to be a benefit in increasing moisturization in the ocular area due to the presence of the polymer itself.

It is important to remember that the polymer remains on the surface of the skin and gradually releases the entrapped vitamins for penetration through the stratum corneum, into the epidermis and the dermis; the rate of release from the polymer and, therefore, entry into the skin is determined by the interaction between the active ingredients in the polymer, the remainder of the base, and the stratum corneum.<sup>8</sup>

#### CLINICAL STUDY

Thirty subjects met the criteria for entry into the study. They were obtained from the general population of the Dermatology Center in Nashville and from solicitation by newspaper advertising for individuals with dark circles. Subjects could be male or female, over 18 years of age, non-users of Retin-A, glycolic acid and topical vitamin

C, must agree to participate in the study for a period of at least 16 weeks, allow photographs to be obtained, and to undergo no cosmetic procedures of any type during the course of the study. Observations were made after 2, 4, 8, 12, and 16 weeks of treatment. At these times, the subjects were observed and questioned for potential side effects and photographs of both eyes were obtained.

Since no other treatment had previously been shown to be effective for dark circles, the subjects and the baseline photographs served as their own controls with global evaluation by the subjects and comparison of the photographs at baseline and 16 weeks by the investigator to determine the degree of benefit from application of the cream.

Participants were to apply the cream on moist skin to the lower and lateral eyelid area at bedtime, using a small amount, about the size of a grain of rice. No other treatments or moisturizers were allowed and only cleansing with a provided mild cleanser (Cetaphil) and foundation were allowed to be used in the morning.

One subject dropped out because he could not keep his scheduled visits and a second developed irritation. This subject was closed patched-tested to the cream and the test was negative at 72 hours, but she developed dryness and irritation when she attempted to use the cream. Some individuals developed dryness and slight irritation during the initial week of use. However, by instructing the subjects to make certain that they used a small amount of material and on moist skin, it was possible for them to continue without irritation being a problem. At the end of the study, two participants were not certain there was a significant improvement with the treatment, but the other 26 (93%) rated the cream successful in alleviating their dark circles by direct evaluation. Based on the investigators' evaluation of photographs obtained at baseline and at 16 weeks, as well as observation of the patients, the formulation was found effective in treating dark circles under the eyes.

TABLE 1

#### DARK CIRCLES REDUCTION - ASSESSMENT FROM PHOTOGRAPHS

	Mean Score* ± SD	% Reduction	P
Baseline	14 ± 5.2	-	-
2 weeks	11.6 ± 5.3	17	<0.02
4 weeks	10.4 ± 5.8	26	<0.01
8 weeks	9.4 ± 4.2	33	<0.01
12 weeks	7.5 ± 3.2	46	<0.01
16 weeks	6.2 ± 2.0	56	<0.01

\* mean of total dark circle scores of 11 subjects



## Periorbital Hyperpigmentation



Fig. 4a: 28-year-old white male at baseline.



Fig. 4b: Same patient, 16 weeks later.

(Figures 3a-b & 4a-b are representative photographs of subjects during the study.)

Two independent expert graders reviewed all the photographs obtained in the study. Some of the photographs were considered inadequate for technical reasons. In addition, not all of the subjects completed all the observations, or they returned at various intermediate times that did not coincide with the stipulated ones.

For these various reasons, 11 subjects were considered evaluable for quantification by expert graders. For each one of these subjects, two photographs of the left eye (front and side view) and two of the right eye were selected for each observation point.

A 10-point analog scoring scale was used for evaluation where "0" was defined as no difference between the color of the skin under the eye and that of the rest of the face and "10" was considered to be a point with severe (maximum imaginable) darkness in the area surrounding under the eye.

The photographs were randomly projected onto a screen and scored separately by the two graders.

These total scores were tabulated, added for each observation time, and a mean score was calculated. These are presented in Table 1. Statistical significance of the reduction at various observation times mean score vs. the baseline mean score was calculated by a related sample t-test. Reduction in darkness mean scores were statistically significant ( $p < 0.05$ ) at each and all observation points.

### SUMMARY

In summary, a topical formulation containing 1% phytonadione and 0.15% retinol that utilizes a patented delivery technology to provide slow gradual release into the skin provides significant improvement in the appearance of periorbital hyperpigmentation (dark circles under the eyes) without any important side-effects. Twenty six out of 28 (93%) of the patients achieved benefits as determined by patient self-evaluation and investigator evaluation of the photographs at the beginning and the end of the time period of use of the cream. When photographs from a sub-group of these subjects

obtained at various intermediate times were evaluated and quantified by two independent observers, the changes from baseline were found to be statistically significant at all observation times. ■

Disclosure of Interest: Dr. Elson holds the patent for topical Vitamin K, and receives royalties from Advanced Polymer Systems for topical Vitamin K.

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