

The Evaluation of the Efficacy of Derivatives of Vitamin K

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Abstract

Objectives: The aim of the study was to evaluate the safety and effectiveness of cosmetic products containing two derivatives of vitamin K on skin with vascular problems.

Materials and methods: The study was conducted in two groups, 24 people, and the other included 22 participants, mean age 50. The participants applied creams twice a day for a period of 4 weeks. Creams were applied on the right half of the face-concentration of 0.5% and 0.1%-on the left. The participants completed a questionnaire and a measurement was performed using standardized equipment Multi Probe Adapter (MPA) Courage-Khazaka and VISIA Canfield.

Results: Application creams with MQ and Epoxy MQ derivatives at a concentration of 0.1% and 0.5% had the effect of reducing redness of the skin at a comparable level. All of formulations did not contribute to decrease melanin level. The hydration was increased after application MQ (0.1% and 0.5%) adequately 14% and 13% in about 60% participants. The elasticity was significantly improved in all groups.

Conclusion: Derivatives of vitamin K such as Epoxy MQ and MQ used in 0.1% and 0.5% give comparable results reducing redness of the skin. The improvement of erythema was more significant with 0.1% concentration (MQ and Epoxy MQ).

Keywords: Vascular skin; Erythema; Vitamin K; Cosmetic formulation; Teleangiectasia

Introduction

Dermocosmetics are especially designed to treat facial skin problems of various etiology. Capillary skin problems more and more frequently affect middle-aged people. Such lesions are mostly situated on cheeks, nose and chin. Transient flushing is a predominantly observed sign. Additionally, characteristic skin lesions such as teleangiectasias and permanent erythema may develop on the central facial area. The pathophysiology of these features may be associated with impaired vasomotor system functions, responsible for constriction of blood vessels. The formation of characteristic skin lesions may be triggered by environmental and lifestyle factors such as stress, sun exposure, frequent temperature changes, hot meals and alcohol consumption. Unfortunately, exact pathophysiology of transient and persistent erythema still remains unknown. In consequence, the presence of facial redness may impair the emotional well-being of patients, embarrass them and decrease their self-esteem and self-awareness. Moreover, people with facial redness often tend to withdraw from social contacts [1].

Vitamin K is a fat-soluble vitamin and it occurs in 3 forms, i.e. Vitamin K1 (Phylloquinone, Phytonadione), Vitamin K2 (Menaquinone) and Vitamin K3 (Menadione). The most common

form is Phylloquinone and it can be found in green vegetables and vegetable oil; vitamin K2 is found in animal products, whereas Menadione has an artificial source. A lot of studies indicate that long-chain menaquinones have a longer half-life, which makes them more bioavailable [2]. Vitamin K is involved in a series of biochemical transformations in the liver. Its most prominent function is the role of a cofactor for gamma-glutamyl carboxylation of certain glutamate (Gla) residues which are present in coagulation factors II, VII, IX, X. Vitamin K antagonists contribute to suppressing carboxylation of coagulation factors and lessening blood coagulation. Extra-hepatic Gla-proteins appear in osteocalcin (known as bone gamma-carboxyglutamic acid-containing protein) and in the vascular wall (as matrix Gla-protein). The Gamma-glutamyl carboxylase enzyme is activated by vitamin K; it initiates the coagulation cascade and leads to formation of a blood clot. GGC is located in the liver, pancreas, spleen, kidney, thymus, fibroblasts and cancer cells of different origin. Moreover, proteins containing Gla residues are involved in the regulation of coagulation action, have an impact on metabolism of bones and blood vessels and prevent calcification of blood vessel [3]. Vitamin K2 is engaged in bone formation by stimulating osteoclast activity and carboxylation of osteocalcin [4]. High intake of vitamin K prevents from arterial calcification, coronary heart diseases and plays an important role in reducing the risk of prostate cancer [5].

Only recently vitamin K in cosmetics used for treatment of vascular skin. For a long time it was considered a vitamin K-dependent enzyme

(gamma-glutamyl carboxylase), exclusively active in the liver. Hence, vitamin K was administered only orally. Due to the presence of this enzyme in the skin, the method of administration changed. Vitamin K, contained in cosmetics has an impact on Gamma-glutamyl carboxylase, accelerates the blood coagulation process and makes dilated blood vessels less visible. Additionally, vitamin K strengthens blood vessel walls and decreases their fragility [6].

Capillary skin requires complex and holistic care. Appropriate facial skin care involves minimizing exposure to external and internal factors which contribute to the emergence of vascular changes. Active ingredients contained in cosmetic formulations should strengthen blood vessels, make skin lesions less visible, have anti-inflammatory and anti-clotting properties. Vitamin K could be one of such ingredients. The aim of the study was to evaluate the safety and effectiveness of cosmetic products containing two derivatives of vitamin K, encoded as MQ and Epoxy MQ in two concentrations on skin with vascular problems.

Materials and Methods

The study was conducted in two groups. The first one consisted of 22 people (Test 2 and 2A of MQ derivate), and the other one included 24 people (Test 3 and 3A of epoxy MQ derivate). All the participants had vascular lesions. The mean age of the people included in the test was 49. Volunteers were selected in accordance with the guidelines of the Helsinki Declaration. Consent for the study was given by the Ethics Commission of the Medical University of Lodz (RNN/268/15/KE). Cosmetic formulations were tested in the following manner: a product containing 0.5% of vitamin K derivate was applied on the right half of the volunteers' faces, whereas on the left half of the face the volunteers were applied a product containing 1% of vitamin K derivate. All the participants used the creams twice a day for a period of 4 weeks. The skin parameters were measured before, and after 4 weeks (D0 and D28 respectively). In the present study, we used *in vivo* techniques (corneometer, mexameter, cutometer and VISIA®) to evaluate the outcome of the tested cosmetic formulations on the skin tone, hydration and elasticity. In addition, the participants filled in a survey in which they gave a subjective evaluation of the effect. During the study all the participants were provided with dermatological consultations.

The inclusion criteria for testing the creams were the occurrence of redness and dilated blood vessels on the face. The exclusion criteria were viral infection, bacterial and fungal infections, pregnancy and breastfeeding, acute and chronic inflammation on the face, sun exposure and use of cosmetics or other oral formulations which seal blood vessels and contribute to skin lightening. An analysis of effectiveness of cosmetics was carried out on the base of objective measurements, made by Multi Probe Adapter (Courage-Khazaka Electronic GmbH, Cologne, Germany) and a subjective survey. All measurements were taken in a measuring room with controlled humidity (H=30%-50%) and temperature (T=19°C-21°C) [7]. Corneometer® CM 825, included in the MPA580 device, was used for measuring the degree of hydration of the stratum corneum. Thanks to the device, the average capacitance of the dielectric was measured. The probe measures the moisture at a depth of about 10-20 µm [8].

Mexameter® MX probe 18 is designed to perform a simultaneous measurement of the level of melanin-dye responsible for skin pigmentation as well as hemoglobin, i.e.-pigment, responsible for the colour of blood. The latter blood component might cause skin redness.

The Mexamater® is based on the analysis of two physico-chemical phenomena-absorption and reflection of light. The probe sends three waves of the following lengths: $\lambda=568$ nm-green, $\lambda=660$ nm-red and $\lambda=870$ nm-infrared. The obtained result indicates the level of erythema and melanin [9].

Cutometer® measures the elasticity (R2) and firmness (R0) of the skin. The device operation involves creating vacuum inside the device. The device has an in-built optical measuring system, consisting of the source and receptor of light, and the two prisms are located opposite each other. Light covers the distance from the transmitter to the receptor. Resistance of the skin, induced by the action of the vacuum, and the time needed to return to a resting state, is a measure of the elasticity of the skin. The measurements that we made allowed us to obtain the following values:

- R0-is used to determine the firmness of the skin. This is the passive behaviour of the skin, measured at the time of the maximum amplitude.
- R2-determines skin elasticity gross-it is a measure of its overall flexibility. In other words, it regards resistance to deformation and predisposition to return to its original state.

Five participants of test 2 and 2A and 3 participants of test 3 and 3A had a photographic documentation taken by VISIA®. The VISIA Complexion Analysis System allowed monitoring the progress of treatment with topical vitamin K. The photographic system VISIA® takes pictures of the left and right profiles, and the entire surface of the face. By comparing images before and after the therapy, we can perform a detailed analysis of the same area of the face and evaluate the efficacy of the therapy. Besides, the results are compared to results of statistical data regarding a particular population, race, gender and age. The data introduce results and the number of features present. The amount of features only show the number of changes without considering their size and intensity. The VISIA system generates a series of photographs using standard, ultraviolet and cross polarized lighting-RBX®. Canfield's patented RBXTM (Red/Brown/X) technology provides assessment of the amount of melanin and hemoglobin content. The hemoglobin serves as a measure of the amount of redness in the skin, including erythema, vascular lesions and telangiectasias [10].

Results

Questionnaire results

The results of the survey demonstrated that tested creams did not cause adverse reactions manifesting with redness, burning, itching, papules and pustules any other alarming changes that might indicate skin sensitization. Preparations were very well tolerated by sensitive and vascular skin. All of the participants were also satisfied with the use of the cosmetics, the vast majority of respondents expressed the desire to use them in the future.

Subjective assessment showed positive changes in reducing: redness, the presence of dilated capillaries and feeling of tension and irritation of the skin. Creams provided the feeling of skin softness and freshness. Over 50% of the respondents stated that the creams have not reduced hypersensitivity of the skin to external factors such as sudden temperature change, stress, alcohol and hot spices. 40% of the participants noticed dark circles and bags under the eyes became less visible (Figure 1 and 2).

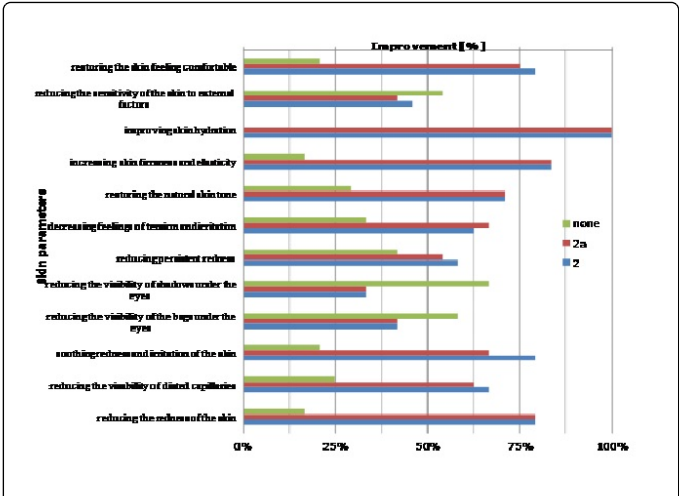


Figure 1: Subjective assessment of the efficiency of applied cosmetics with MQ in test 2 (0.1%) and 2A (0.5%) after 4 weeks.

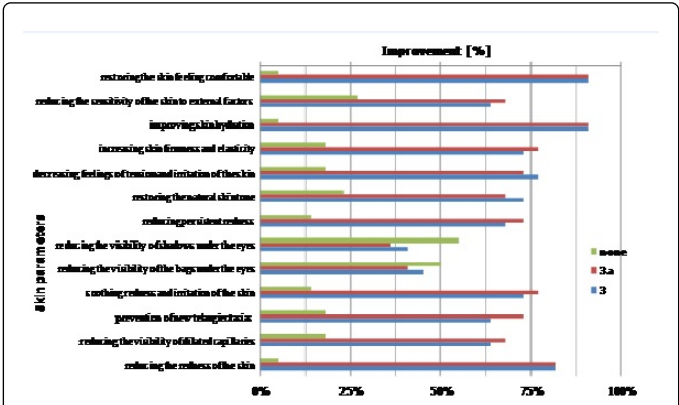


Figure 2: Subjective assessment of the efficiency of applied cosmetics with Epoxy MQ in Test 3 (0.1%) and 3A (0.5%) after 4 weeks.

level of melanin remained unchanged. Skin hydration increased only in test 2 and 2a by 15% in 60% patients. Elasticity improved by 20% in all groups, but the most significant improvement was noticed in Test 3 and 3a (Table 1). VISIA analysis indicated significant reduction of red areas (Table 2 and Figure 3).

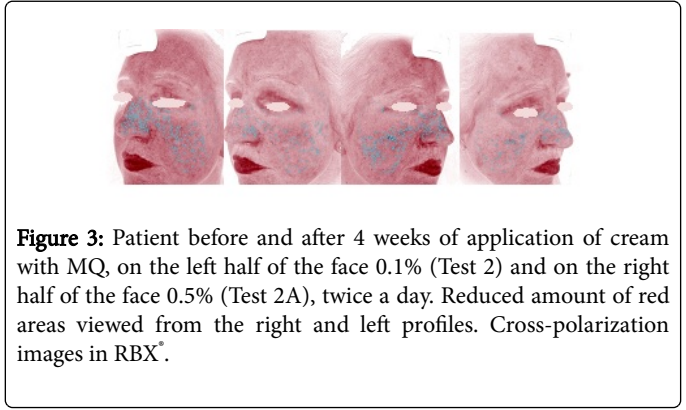


Figure 3: Patient before and after 4 weeks of application of cream with MQ, on the left half of the face 0.1% (Test 2) and on the right half of the face 0.5% (Test 2A), twice a day. Reduced amount of red areas viewed from the right and left profiles. Cross-polarization images in RBX°.

Parameters of skin condition	Test 2 with 0.1% MQ after 4 weeks	Test 2A with 0.5% MQ after 4 weeks	Test 3 with 0.1% Epoxy MQ after 4 weeks	Test 3A with 0.5% Epoxy MQ after 4 weeks
Skin tone (erythema)	decrease by 14% in 71% participants	decrease by 14% in 63% participants	decrease by 12% in 77% participants	decrease by 15% in 73% participants
Skin tone (melanin)	lack of improvement	lack of improvement	lack of improvement	lack of improvement
Hydration	increase by 14% in 58% participants	increase by 13% in 67% participants	lack of improvement	lack of improvement
Elasticity	increase by 24% in 71% participants	increase by 21% in 88% participants	increase by 26% in 68% participants	increase by 23% in 73% participants

Table 1: Analysis of the skin condition after 28 days of treatment (Test 2, 2A, 3, 3A).

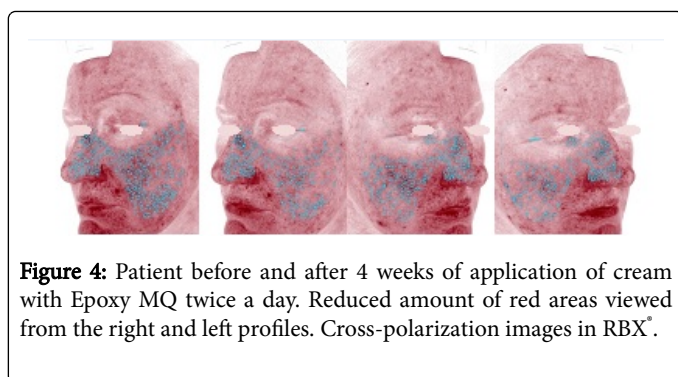
Result of instrumental analysis of skin condition

Skin color measured by the Mexameter® MX18 showed amount of erythema was reduced by nearly 15% in 75% patients in all tests. The

	Parameters of skin condition	Test 2 with 0.1% MQ , after 4 weeks	Test 2A with 0.5% MQ, after 4 weeks	Test 3 with 0.1% Epoxy MQ after 4 weeks	Test 3A with 0.5% Epoxy MQ after 4 weeks
VISIA-redness	Red areas	decrease by 27% in 60% participants	lack of improvement	decrease by 17% in 60% participants	decrease by 11% in 80% participants

Table 2: Results of measurements using VISIA®.

A comparative analysis carried out by means of VISIA® showed a more significant reduction in the number of red areas on the left facial profile. A study of the effectiveness of cosmetics with different derivatives of vitamin K revealed that creams containing a lower concentration of active substance made the therapy more effective (Table 3 and Figure 4).



Test 2 and 2A-MQ derivatives			
Location	Amount of red areas before application	Amount of red areas after 4 weeks	Disparity after 4 weeks
Left profile (0.1%-test 2)	191	95	96
Right profile (0.5%-test 2a)	174	94	80

Table 3: Results of measurements using VISIA® of patient shown on Figure 3 tested 0.1% (test2) and 0.5% (test 2A).

Test 3 and 3A-derivatives MQ			
Location	Amount of features before of application	Amount of features after 4 weeks	Disparity after 4 weeks
Left profile (0.1%-test 2)	316	204	112
Right profile (0.5%-test 2a)	251	204	47

Table 4: Results of measurements using VISIA® patient shown on Figure 4 tested 0.1% (Test 3) and 0.5% (Test 3A).

Discussion

Facial skin redness is a common aesthetic problem. Vascular skin is an equally frequent and embarrassing condition, especially for women, and is associated with age. The pathogenesis of vascular skin might be related to genetic, hormonal and environmental factors. Moreover, alcohol, stress, eating spicy meals, drinking hot drinks and excessive sun exposure predispose to occurrence of skin lesions [11].

The main objective of the study was to measure efficacy and safety of cosmetic products, containing derivatives of vitamin K, on capillary skin condition. In order to verify subjective satisfaction with application of cosmetics with vitamin K, the authors conducted a survey. Cosmetic formulation had been created to improve the condition of blood vessels and decrease redness. The authors analyzed different biologically active derivatives of vitamin K, used in various concentrations and compared the effectiveness of their action. The total quantity of active substance was unusually low in contrast to the number of cosmetic products, currently available on the market. Undoubtedly, an application of a lower concentration of active

substance reduces the risk of side effects, such as irritation, rash, itching, burning and hyperpigmentation. Derivatives of vitamin K (MQ and Epoxy MQ) were examined in creams in concentration 0.1% and 0.5%. An *in vivo* analysis confirmed that the derivatives effectively reduce erythema and additionally, improve hydration and elasticity of the skin.

Anti-redness treatment has a significant impact on capillary skin. One of the most common ways to reduce facial redness is using Intense pulsed light Therapy (IPL). A study by Hassan et al. evaluated the efficacy of the IPL treatment. Measurement performed after four IPL treatment sessions revealed substantial reduction of erythema [12]. The efficacy of the PDL therapy in reducing erythema and strengthening blood vessel was analyzed by Kim et al. [13]. Beauty treatments are alternative methods of reducing vascular lesions. Neuhauser et al. compared the efficacy and safety of IPL and PDL treatments in rosacea. Both treatments contributed to a significant improvement, but the difference between the treatments was insignificant [14].

High price of beauty procedures, contradictions and frequent occurrence of side effect are limiting factors to the light therapy. In response to great demand, cosmetic industry looks for innovative methods which would reduce facial skin redness. Application of products with vitamin K proved to be alternative methods to reduce redness, skin color and improve elasticity. A randomized study by Hemmati et al. confirmed that vitamin K1 strengthens blood vessels, increases an amount of fibroblast cells, collagen fibers, improves skin tone and reduces redness [15]. Cream containing 1% phytonadione and 0.15% retinol was tested by Melvin et al. Photographs show a significant decrease in the amount of periorbital dark circles [16]. Ahmadrabi F. et al. tested 1 eye counter pad with 1% vitamin K and caffeine. They noted that the amount of dark circles and depth of wrinkles decreased and skin elasticity improved [17].

A study conducted by Shah et al. compare the efficacy of cream with vitamin K compared with pre-treatment or post-treatment pulsed dye laser therapy. The post-treatment laser therapy significantly reduces bruising [18]. Derivatives of vitamin K have comprehensive application in medial and cosmetic field. Lou et al. examined the safety and efficacy of vitamin K creams in shortening the duration of laser-induced purpura. Cream containing 1% vitamin K and 0.3% retinol contribute to hasten the occurrence of laser-induced purpura [19].

The effectiveness of active substance is associated with a selection of appropriate cosmetic formulation. Campani et al. tested vitamin K in different cosmetic formulation. The study compare effectiveness liposome-base formulation for VK1 before or after being nebulized with a fatty ointment with VK1. The results perform increase enhanced VK1 accumulation in epidermis and dermis when compared with a marketed VK1-containing fatty ointment. It suggested that the newly developed formulation can be considered a valid alternative to fatty ointments [20]. A randomized study by Lopes et al. demonstrated differences between accumulation and transdermal penetration of vitamin K, containing three diverse lipid formulations. Numerous scientific studies have shown that the effectiveness of active ingredients is dependent on the selection of appropriate penetration promoters, which facilitate intercellular transport [21].

Many active substances are also used in cosmetics for vascular skin. Khan et al. tested derivatives of vitamin C present in many cosmetic formulations. The amount of melanin and erythema was decreased [22]. Serum tested by Dupton et al. consisted of active substances, such

as retinol, ascorbic acid, bisabolol and tocopheryl acetate. These substances have anti-redness and anti-age properties. A visual evaluation, photographs and colorimetric analyses confirm a significant decrease in the level of erythema. Besides, vitamin K improved hydration and skin elasticity [23]. Many studies confirm that low concentrations of vitamin K reduce severity of side effects and skin irritation [24,25]. All of the mentioned studies confirm the efficacy of vitamin K in reducing redness. Sensitive and vascular complexion requires a holistic approach.

Conclusions

Different derivatives of vitamin K effectively reduce erythema and improve skin tone. Moreover, skin hydration and elasticity improve after treatment. An analysis of the efficacy of vitamin K in cosmetics and medical preparations confirms a positive influence on skin texture. Different derivatives of vitamin K, such as Epoxy MQ and MQ, used in 0.1% and 0.5% concentrations significantly decreased red areas and demonstrate their anti-aging effects.

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