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Improvement in skin wrinkles with use of a preparation containing human growth factors and hyaluronic acid serum

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Abstract

BACKGROUND

Skin aging is accompanied by wrinkle formation. At some sites, as the periorbital skin, this is a relatively early phenomenon.

OBJECTIVE

We evaluated the anti-wrinkle effect of a preparation containing human growth factor and hyaluronic acid serum on periorbital wrinkles (crow's feet).

MATERIALS AND METHODS

In all, 23 Korean women (age range: 39-59 years), who were not pregnant, nursing, or undergoing any concurrent therapy were enrolled in this study. All the patients completed an 8-week trial of twice daily application of human growth factor and hyaluronic acid serum on the entire face. Efficacy was based on a global photodamage score, photographs, and image analysis using replicas and visiometer analysis every 4 weeks. The standard wrinkle and roughness parameters used in assessing skin by visiometer were calculated and statistically analyzed.

RESULTS

Periorbital wrinkles were significantly improved after treatment, with improvements noted both by physician assessment and visiometer analysis.

CONCLUSION

Topical application of human growth factor and hyaluronic acid was beneficial in reducing periorbital wrinkles.

Introduction

Aging skin is closely associated with chronic sun exposure and is histologically characterized by loss of epidermal polarity, a basket weave appearance of the epidermis, keratinocyte atypia, and reduction and alteration in collagen.[1] Clinically, photoaging manifests with fine and coarse wrinkling, thickening, inelasticity, dryness, roughness, shallowness and pigmentary mottling.[2] Periorbital wrinkle formation is a relatively early sign of skin aging that usually makes women strongly apprehensive. Very few cosmetic preparations were shown to improve this situation using objective quantitative methods.

The present study reports on a preparation consisting of human growth factors and hyaluronic acid serum. A previous study using human growth factor cream showed improvement of facial skin aging after a 2-month application period. Topical growth factor repaired UV-damaged skin *in vivo*, leading to wrinkle effacement.[3] Another study using topical hyaluronic acid cream revealed a significant reduction in wrinkle depth.[4]

The purpose of this study is to evaluate the effectiveness of a novel combination of human growth factor and hyaluronic acid in reducing periorbital wrinkles.

Materials and methods

Subjects

Twenty-three generally healthy Korean women between 39 and 59 years of age were selected from volunteers. All patients satisfied the inclusive criteria of periorbital wrinkles (global photodamage score 1~6)[5] confirmed by a dermatologist's physical examination. Thirteen patients had mild photodamage (grades 2–3 on a 0–7 scale), and 10 had moderate photodamage (grades 4–6 on a 0–7 scale). None of the women had used topical agents to treat their photodamaged areas within 3 months prior to this study. None of the women had undergone wrinkle removal or peeling procedures within 6 months prior to the study. None of the women were pregnant or breastfeeding or had atopic dermatitis, allergic diathesis, or hypersensitive skin. The study was approved by the relevant institutional review boards. All subjects signed informed consent forms, and the study protocol followed the guidelines set forth by the Declaration of Helsinki and Korean Good Clinical Practice.

Study design

Before beginning the study, subjects were permitted to apply their usual brand of cosmetics provided these products did not contain any ingredients known to affect skin rejuvenation. Subjects received a topical preparation containing human growth factors and hyaluronic acid

(Nutrex, Inc., Seoul, Korea) and sufficient sunscreen agents. Human growth factors are composed of rh-Oligopeptide-1 (EGF), rh-Polypeptide-1 (bFGF), rh-Polypeptide-3 (KGF-2), rh-Polypeptide-28 (SOD1), rh-Oligopeptide-2 (IGF-1), and human stem cell conditioned medium (HSCM). In the morning and evening, each subject applied approximately 1.0 g of the test product to her entire face (total daily product usage ~2 g). Subjects received the containers of test product at baseline and returned used containers at week 8. Subjects recorded each application of the test product in a diary. Compliance with the product regimen was assessed via diary records and the weight of returned containers. The participants were instructed to apply sunscreen after the study product if needed.

Clinical evaluations were made at weeks 0 (baseline), 4, and 8. Visual assessment by a dermatologist, photographs obtained from each subject, and image analysis of replicas using a visiometer (Skin-Visiometer SV 600; Courage-Khazaka Electronic, Cologne, Germany) were used to analyze changes in skin wrinkles.

Efficacy and safety assessments

Two blinded dermatologists evaluated subjects' periorbital wrinkles. The dermatologists evaluated periorbital wrinkles using a global photodamage score (Table 1) at weeks 0 (baseline), 4, and 8.[5] If the dermatologists' evaluations differed, low-grade efficacy and high-

grade adverse effect was selected. Subjects' periorbital wrinkles were classified into eight grades. The investigator recorded adverse effects such as erythema, edema, scaling, itching, stinging, burning, tightness and prickling.

Wrinkle improvement was evaluated by measuring skin roughness and wrinkles using the Skin-Visiometer SV 600.[6] Replicas of right and left periorbital areas were taken at weeks 0 (baseline), 4, and 8. Skin replicas of crow's feet were obtained according to the technique reported by Grove *et al*.[7] and analyzed with visiometer software. Evaluations were performed in the same location with the same lighting at each visit. Parameters used in the assessment of skin with the Visiometer SV 600 were as follows: R1, skin roughness; R2, maximum roughness; R3, average roughness; R4, smoothness depth; and R5, arithmetic average roughness.

Statistical analysis

All data were analyzed using the Bonferroni method with SPSS software version 19.0 (SPSS, Inc., Chicago, IL, USA). In all cases, differences were considered statistically significant when $p < 0.05$.

Results

All twenty-three subjects completed the study. No subjects discontinued their participation due to lack of effectiveness or adverse events. On average, the subjects consumed 85–95% of the amount of test product expected.

The average photodamage score of all patients significantly improved (Table 2). This score decreased from 3.30 (baseline) to 3.13 (4 weeks, $p = 0.046$), and to 2.83 (8 weeks, $p = 0.002$ vs. baseline). Figures 1 illustrates remarkable improvements in periorbital wrinkles after 8 weeks.

Figure 2 compares five visiometer parameters at weeks 4 and 8. Visiometer R-values R1 through R5 decreased as wrinkles diminished. Skin roughness (R1), maximum roughness (R2), and average roughness (R3) showed statistically significant differences at weeks 4 and 8. At week 8, every R-value showed statistically significant differences.

The test product was well tolerated by all subjects. None of the participants reported any serious adverse events.

Discussion

Chronic UV exposure leads to changes in the physiological and biochemical features of the skin. Clinically, photoaging skin is characterized by wrinkled, dry, inelastic and irregularly pigmented skin. These characteristics usually result from the increase of epidermal thickness, and reduction in collagen in the dermis.

As concern about aging and interest in rejuvenation has been increasing, various anti-wrinkle products have been researched and developed. Many topical cosmetic products are reported to decrease the appearance of wrinkles. Some of these products work by expanding the dermis with hydration. As dermal expansion allows the epidermis to spread out, wrinkles are temporarily smoothed and their appearance is reduced. However, more efficacious cosmeceutical products, such as human growth factors, create lasting dermal expansion by stimulating the regeneration of the dermal components that have been lost to aging, such as collagen and mucopolysaccharides.[8]

Topical application of growth factors is known to promote the development of keratinocytes, dermal fibroblasts, and other cells with decreased proliferative capacity due to aging. In addition, some growth factors are potent stimulators of the expression of extracellular matrix proteins, including collagen.[9] Hyaluronic acid is a major component of the extracellular matrix of the skin and plays an important role in the metabolism of the dermis.[10] Hyaluronic

acid is proposed to help the skin to retain and maintain elasticity, turgor, and moisture because photoaged skin has been shown to be characterized by reduced levels of hyaluronic acid.[4]

The present study demonstrated a significant improvement in the treatment of photoaging-induced wrinkles using the topical application of human growth factors and hyaluronic acid serum in women with facial photodamage. Clinical data based on investigator assessment revealed a greater improvement in periorbital wrinkles. In this clinical study, the overall average photodamage scores significantly improved with the novel combination agent. An objective technique using replicas and visiometer analysis also showed statistically significant differences in all R-values after 8 weeks. This result correlates well with the clinical findings.

The preparation in this study showed great safety as a cosmeceutic in humans; none of the participants reported any adverse effects. This topical agent may be an excellent candidate for wrinkle control without the negative side effects commonly associated with many other skin rejuvenating agents.

EGF, bFGF, KGF-2, SOD1, and IGF-1, the growth factors in the test preparation, are used as anti-aging agents. These growth factors may promote cell development, which is typically decreased due to aging, and stimulate collagen formation. Because EGF can make skin cancer grow more quickly, careful cautions are required to patients who have suspicious skin lesions.

Hyaluronic acid supports the tissue architecture of the extracellular matrix, determines skin elasticity, is involved in cell migration and differentiation processes, and might act as an antioxidant due to the restriction of movement of reactive oxygen species.[11] Hyaluronic acid may protect growth factors from degradation by proteases, making hyaluronic acid and growth factor a promising combination.[12] There is also some evidence that hyaluronic acid and growth factors act synergistically to accelerate the healing process.[13] Therefore, topical products with hyaluronic acid in combination with human growth factors might be particularly well suited to skin rejuvenation.

Because this study was not designed as case-control study or a split-face study due to ethical issues, it is not possible to assess definite results. Also, further long-term follow-up studies are required. Additionally, epidermal and dermal changes were not examined before or after the treatment. Despite these limitations, the reported data suggest that this preparation containing a combination of human growth factors and hyaluronic acid reduced the appearance of periorbital wrinkles. This study demonstrates the importance of careful selection of ingredients when formulating cosmetic products to improve the appearance of skin wrinkles.

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Tables

Table 1. Global photodamage score.

Score	Degree
0	None
1	None / mild
2	Mild
3	Mild / moderate
4	Moderate
5	Moderate / severe
6	Severe
7	Very severe

Table 2. The average global photodamage score as assigned by the evaluating investigator.

Visit	Global photodamage score	*P*-value (vs. baseline)
Baseline	3.30 ± 1.22	
4 weeks	3.13 ± 1.14	0.046 *
8 weeks	2.83 ± 0.78	0.002 *

*$p<0.05$

Figure legends

Figure 1. Clinical photographs of wrinkles before and after treatment. Improvement of periorbital wrinkles (a, b) is noticeable.

Figure 2. Changes in wrinkles were analyzed by the Skin Visiometer SV 600 after 4 and 8 weeks treatment. R1, skin roughness; R2, maximum roughness; R3, average roughness; R4, smoothness depth; and R5, arithmetic average roughness.

Figure 1. Clinical photographs of wrinkles before and after treatment. Improvement of periorbital wrinkles (a, b) is noticeable.
161x127mm (150 x 150 DPI)

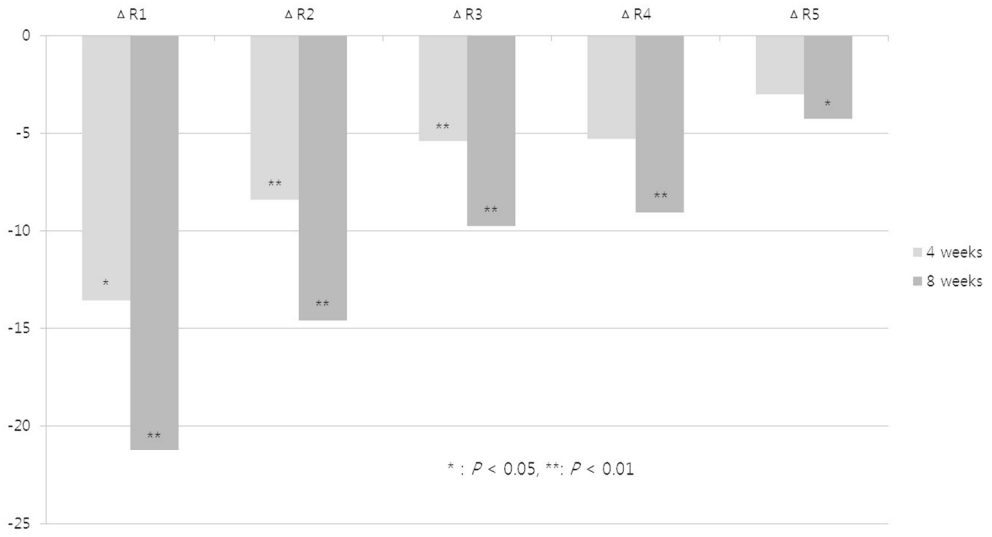

Figure 2. Changes in wrinkles were analyzed by the Skin Visiometer SV 600 after 4 and 8 weeks treatment. R1, skin roughness; R2, maximum roughness; R3, average roughness; R4, smoothness depth; and R5, arithmetic average roughness.
228x125mm (150 x 150 DPI)