CLINICAL EVALUATION OF THE EFFECT OF A NOVEL BI-MINERAL COMPLEX ON PERIORBITAL SKIN

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INTRODUCTION

Elastin is a protein polymer responsible for the stretch and recoil properties of skin and other tissues. It is composed of water-soluble tropoelastin protein molecules (monomers) that are joined to each other by desmosine and isodesmosine cross-links. This crosslinking is critical in facilitating the recoil of stretched elastin.

Unlike collagen, elastin is capable of lasting the entire human lifespan and is primarily synthesized during late gestation and early childhood. It is never turned-over in skin and cannot be correctly synthesized after early adulthood. Hence, loss of or damage to cutaneous elastin, due to intrinsic factors (eg, normal aging) or extrinsic factors (eg, chronic exposure to UV light), results in nearly permanent loss of elasticity giving rise to lax skin accompanied by rhytides in facial skin. Periorbital skin is particularly prone to such loss of elasticity and the development of hyperkinetic lines.

Some coordination minerals, such as copper and zinc, appear to be involved in maintaining the structure and function of the skin and could have potential as therapeutic agents. Copper, for example, is a cofactor for the enzyme, lysyl oxidase, which catalyzes the synthesis of desmosine cross-links in elastin from four lysine amino acids on four different tropoelastin molecules.[1] Zinc is well-known for its wound-healing characteristics.

Previous clinical studies have demonstrated that topical application of a novel bi-mineral complex can increase both the number and density of dermal fibroblasts (which synthesize collagen and elastin) and the deposition of elastic fibers in photoprotected skin.[2]

The study presented here sought to discover the cellular and molecular effects of the novel bi-mineral complex on photoaged periorbital skin. Quantitative biochemical assessment of cutaneous elastin and collagen as well as histological evaluation of periorbital biopsies are presented.

METHODS

Key inclusion criteria

- Healthy female volunteers at least 50 years of age
- At least Type III skin according to the Glogau Photoaging Classification (advanced photoaging including wrinkles at rest, obvious dyschromia or telangiectasia, and visible keratoses)[3]
- No clinically abnormal findings
- No recent history of drug or alcohol abuse
- Willing to avoid exposure to UV light wherever possible

Key exclusion criteria

- Known allergy or sensitivity to any ingredient in study treatment, local anesthetics, latex or vinyl gloves, or other clinical supplies used in study
- Chronic use of antihistamines or anti-inflammatory medications that may interfere with wound healing
- Use of drugs containing coumadin or heparin, or other blood-thinning agents
- Cosmetic procedure (eg, laser resurfacing, chemical peel, dermabrasion) in 6 months preceding study screening visit
- History of facial nerve palsy
- Atrophy or weakness of facial muscles
- Marked facial asymmetry
- Previous surgery, cosmetic procedure (eg, soft tissue augmentation), or scarring in the periorbital area
- Concurrent use of other medicated products on the face
- Infection or skin disorder on the face
- Uncontrolled systemic disease or known infection with the human immunodeficiency virus
- Anticipated need for procedures, surgery, or overnight hospitalization during the study
- Pregnancy, trying to become pregnant, or breastfeeding

Washout periods

- 1 week for topical antibiotics
- 4 weeks for topical retinoids, systemic antibiotics, topical and systemic steroids, and depigmenting products (including hydroquinone, 4-hydroxyanisole, α-hydroxy acids, β-hydroxy acids, and polyhydroxy acids)
- 1 year for systemic retinoids and facial botulinum toxin type A treatment

Treatment

- Subjects applied the novel bi-mineral complex to their face, either once daily or twice daily for 8 weeks.
- 2 mm punch biopsies of periorbital skin were taken at:
  - Baseline (1 cm to 3 cm lateral to the lateral canthus)
  - Week 6 (within 1 cm of the baseline biopsies).
- Facial skin was washed using a gentle cleanser up to 1 hour before any intervention or evaluation.
- Patients were required to avoid applying any other topical products to the treatment area during the study (including make-up, moisturizers, and sunscreens).

Efficacy outcome measures

- Periorbital biopsies were evaluated as follows:
  - Morphological assessment of elastic fibers (after using Hart's stain for elastin)
  - Biochemical assessment of insoluble elastin content (by using a radioimmune assay to assess desmosine, a cross-link found only in insoluble elastin)
  - Biochemical assessment of collagen content (via amino acid analysis to assess hydroxyproline, an amino acid in collagen).
- Standardized photographs were taken at baseline and week 8.

Statistical analyses

- All analyses were conducted on the intent-to-treat population (ie, all randomized subjects who received at least one dose of treatment).
- An alpha level of <.05 was considered statistically significant.

RESULTS

Patients

- Of 23 subjects enrolled, 20 had evaluable results. (Three did not consent to the follow-up biopsy at week 6 and their efficacy data were excluded from the analysis.)
- The subjects' age ranged from 50 to 84 years.
- One subject was Asian and all others were Caucasian.

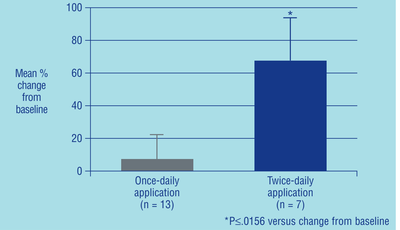
Efficacy

- Twice-daily treatment with the novel bi-mineral complex was associated with increased levels of elastin (Figure 1) and collagen (Figure 2). Once-daily treatment was only minimally effective in increasing elastin.
- Histological assessment suggests that twice-daily treatment resulted in the replacement of clumped and relatively thick elastic fibers by finer and more discrete fibers (Figure 3). Once-daily treatment was only minimally effective in inducing histological changes (Figure 4).
- Photographic documentation confirms that the improvements in dermal biochemistry and histology translate into visible improvements in the appearance of the skin, with a noticeable reduction of periorbital lines after 8 weeks of twice-daily treatment (Figure 5). Once-daily treatment was only minimally effective in inducing visible improvements (Figure 6).

Tolerability

- No adverse events were reported.

FIGURE 1 Mean percent change (± SEM) from baseline in concentration of periorbital skin desmosine (a cross-link, composed of four lysine amino acids, found only in insoluble elastin), after topical application of the novel bi-mineral complex for 6 weeks. Desmosine concentration, in 2 mm punch biopsies of periorbital skin, was determined via a radioimmune assay. Desmosine concentration was normalized per total protein concentration.



*P≤.0156 versus change from baseline

FIGURE 2 Mean percent change (± SEM) from baseline in concentration of periorbital skin hydroxyproline (an amino acid that helps stabilize collagen structure), after topical application of the novel bi-mineral complex for 6 weeks. Hydroxyproline concentration, in 2 mm punch biopsies of periorbital skin, was determined via amino acid analysis and normalized per total protein concentration.

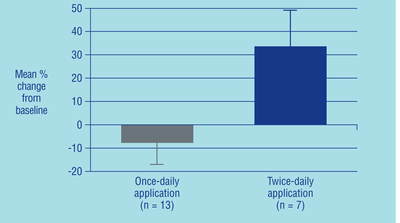


FIGURE 3 Twice-daily applications of the novel bi-mineral complex appear to result in thick and clumped elastic fibers being replaced by finer and more discrete fibers. (Hart's stain was used to visualize the elastic fibers in these periorbital biopsies.)

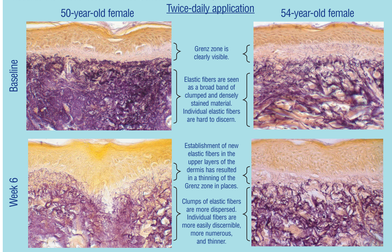


FIGURE 4 Once-daily applications of the novel bi-mineral complex were minimally effective in changing the appearance of elastic fibers. (Hart's stain was used to visualize the elastic fibers in these periorbital biopsies.)

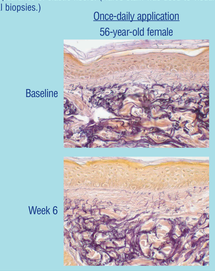
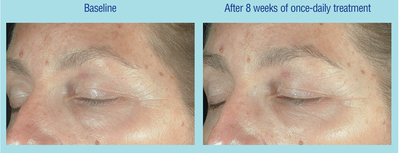


FIGURE 5 Reduction in periorbital lines in a 58-year-old female after 8 weeks of twice-daily treatment with the novel bi-mineral complex.

FIGURE 6 Minimal effect on periorbital lines in a 51-year-old female after 8 weeks of once-daily treatment with the novel bi-mineral complex.



CONCLUSIONS

The results of this study indicate that twice-daily applications of the novel bi-mineral complex to photoaged periorbital skin result in an increase in the level of dermal elastin, and possibly collagen. This is associated with a noticeable improvement in periorbital lines after only 8 weeks of treatment. We believe this is the first topical treatment that demonstrates such improvements in elastin and the results of another study with this product have confirmed that its use significantly enhances the elasticity of the skin.[4]

It appears that the frequency of application of the bi-mineral complex is an important determinant of efficacy, with twice-daily applications necessary for the biochemical, histological, and clinical effects to become clearly apparent. In contrast, once-daily applications were only minimally effective. Further research is required to determine if this threshold of activity varies between different individuals—for example, as a result of skin thickness, genetics, or metabolic disposition. Additional studies are planned to further explore the clinical benefits of this novel product.

REFERENCES

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DISCLOSURES

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