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A Double-Blind Randomized Pilot Study Evaluating the Safety and Efficacy of Topical MEP in the Facial Appearance Improvement of Estrogen Deficient Females

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ABSTRACT

Facial skin aging is accelerated in postmenopausal females due to decreased collagen, reduced hydration, and loss of skin elasticity constituting the characteristics of estrogen deficient skin (EDS). The presence of estrogen receptors on dermal fibroblasts and epidermal keratinocytes confirms the role of estrogen in skin health. This research examined the efficacy and tolerability of topical methyl estradiolpropanoate (MEP) as an anti-aging cosmeceutical with estrogen like cutaneous effects in postmenopausal women who had never taken hormone replacement therapy (HRT). MEP was applied to the face twice daily for 14 weeks but was metabolized in the skin to an inactive compound avoiding estrogen side effects, as demonstrated by the safety study. The efficacy study investigator noted MEP induced statistically significant improvement from baseline at week 14 in dryness (P<0.001), laxity (P=0.001), atrophy (P=0.003), and dullness (P<0.001) as compared to vehicle. Four of nine subjects in the biopsy sub study demonstrated an increase in fibroblasts estrogen receptor staining. The novel concept of a safe and efficacious soft estrogen facial cosmeceutical may provide appearance benefits for postmenopausal women.

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INTRODUCTION

While the benefits of a moisturizer's ability to place a smooth light reflective film over the skin to improve facial appearance are well received by consumers and recommended by dermatologists, there is a need for cosmeceuticals that address underlying physiologic skin changes associated with aging.[1] Accelerated skin aging begins with menopause where women are expected to spend more than one-third of their life.[2] Estrogen loss at menopause results in skin atrophy, decreased collagen content, reduced water content, and loss of skin elasticity characterizing estrogen deficient skin (EDS)[3] The role of estrogen in the skin has been substantiated by the discovery of estrogen receptors in dermal fibroblasts, epidermal keratinocytes, blood vessels, and hair follicles. Additionally, two enzymes involved in estrogen formation, aromatase, and 17 beta-hydroxysteroid dehydrogenase type I are found in the skin.[4]

The loss of skin collagen, resulting in facial wrinkling, may reach 30% in the first 5 years of menopause, with a further decline of 2.1% per postmenopausal year over a period of 15 years. This decline can be prevented with hormone replacement therapy (HRT).[5] Chen et al found HRT treated women had a 10% greater skin thickness than nonsupplemented women.[6] However, HRT is controversial as the Women's Health Initiative trial clearly identified associated risks, such as increased risk of breast cancer, stroke, and thromboembolic disease, with no coronary artery disease benefits.[7] This has led to interest in topical estrogen delivery as a possible safe and efficacious alternative. Topical administration of estradiol for 3 months demonstrated a 38% increase in skin collagen, but other trials have produced less dramatic results.[8] Since estrogen is a drug with side effects, it is not appropriate for use in cosmeceuticals, creating the need for another approach to the antiaging in the estrogen deficient female.[9]

An evolving concept in antiaging medicine is the development of soft drugs. Soft drugs exhibit local action on the tissue to which they are applied due to rapid metabolic inactivation, but do not achieve systemic effects. This concept can also be applied to cosmeceuticals. For example, a soft cosmeceutical can be applied topically to exert an effect, but undergo rapid inactivation with hydrolytic enzymes, such as esterases, that are widely distributed in the blood and other tissues. Thus, the ester form of the cosmeceutical is active in the skin, but it is rapidly converted in the blood to the hydrolyzed carboxylic acid byproducts, which are inactive. This concept has been utilized in the development of methyl estradiolpropanoate (MEP), a synthetic sterol, as a possible anti-aging active ingredient in topical formulation that has estrogen-like cutaneous effects, but is metabolized in the blood to an inactive compound avoiding estrogen side effects.[10] The singular mode of action and inactivation process of this cosmeceutical synthetic sterol indicates that it may have unique value in topical formulations for EDS.

The objectives of this single-site vehicle-controlled double-blinded study were to evaluate the clinical efficacy and tolerability of MEP as compared to vehicle for the management of facial aging in postmenopausal females who had never received HRT.

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Safety Study

An initial safety study was conducted on MEP enrolling 60 females ages 53-80 years who had been amenorrheic for at least 3 years with Rao-Goldman wrinkle classification 3+, Glogau aging classification II-IV, and Fitzpatrick skin type I-IV. Subjects were randomized in a 4:1:1 ratio of MEP plus vehicle to vehicle alone to control moisturizer. The study products were applied twice daily to the entire face for 12 weeks. Blood samples were drawn at baseline and week 12 to obtain plasma for the detection of MEP and the inactive metabolite of MEP (MicroConstants, Inc, San Diego, CA).

No adverse events or safety issues arose during the conduct of the study. The investigator and subject assessed excellent tolerability for MEP plus vehicle. Subjects receiving active topical MEP rapidly converted the soft estrogen to an inactive serum metabolite alkyl carboxylate E161,0,8 insuring the safety of the novel ingredient.

METHODS

The subsequent efficacy study enrolled 80 female subjects age 53-80 years who had been amenorrheic for 3-10 years with Rao-Goldman wrinkle classification 3+, Glogau aging classification II-IV, and Fitzpatrick skin type I-IV who completed informed consent (Concordia IRB, Cedar Knolls, NJ). Subjects did not use HRT currently or in the past. No oral retinoids or topical products containing a retinoid, retinol, or other vitamin A derivative were allowed. Subjects also did not use systemic corticosteroids or any topical facial medications. Facial dermabrasion, microdermabrasion, laser treatments, chemical peels, botulinum toxin or filler/biostimulatory facial injections were not allowed during the study. Topical sunless tanning products, facial waxing, depilatories, alpha-hydroxy acids, salicylic acid, or vitamin C containing products were forbidden.

The investigator and the subjects evaluated overall global facial aging, in addition to a variety of visual signs of facial aging including skin thickness, fine lines, wrinkles, dryness, telangiectasias, laxity, atrophy, dullness, and erythema. The investigator queried the subjects and the subjects also evaluated study product tolerability based on burning and itching. All evaluations were conducted on a 5-point scale: 0=none, 1=minimal, 2=mild, 3=moderate, 4=severe. These study activities occurred at baseline, week 6, week 10, and week 14.

Successfully enrolled subjects were randomized in a 3:1 ratio of MEP plus vehicle to vehicle alone. The vehicle was developed to possess minimal moisturizing qualities to allow a clear independent assessment of MEP skin activity. The constituents of the vehicle were water, glycerin, benzyl alcohol, magnesium aluminum silicate, saccharide isomerate, xanthan gum, phenoxyethanol, and ethylhexylglycerin. This formulation represents thickened water with no occlusive agents to retard transepidermal water loss. Any water attracted by the humectant glycerin would evaporate to the environment. Subjects were instructed to apply the randomized study product to the entire face, avoiding the eyes and mouth, twice daily for 14 weeks. Compliance was determined based on diary entries and product weights.

Nine subjects participated in a biopsy sub-study to evaluate the histologic effects of the MEP active on epidermal thickness (H&E, Cockerell Dermatopathology, Dallas, TX), collagen formation (H&E, Cockerell Dermatopathology, Dallas, TX) and estrogen receptor positivity (estrogen receptor stain, Southwestern University, Dallas, TX). A 3 mm biopsy specimen was obtained from the abdomen at baseline utilizing 2% epinephrine plus lidocaine and suture closure. These subjects were instructed to apply the product to the face and abdomen for the entire study duration followed by a repeat of the abdominal biopsy procedure at week 14.

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Statistical Analysis

The randomized active and control groups were balanced to insure no statistically significant differences in skin aging or demographics were present at baseline. A Mann Whitney two-tailed t test was used to analyze the nonparametric ordinal investigator and subject efficacy and tolerability data. Comparisons were made to baseline longitudinally for intragroup evaluations utilizing a two-tailed Wilcoxon ranked sign test to determine percent improvement in evaluated facial characteristics. Intergroup analysis between the active and vehicle was calculated as difference from baseline utilizing a two-tailed Mann Whitney. Significance was defined as *P* less than or equal to 0.05.

RESULTS

Seventy-nine of eighty females successfully completed the study, with one subject who missed the last visit at week 14 for personal reasons unrelated to the study product. No statistically significant differences in tolerability measurements were noted between the MEP and vehicle arms after twice daily use to the entire face and upper lip for 14 weeks.

At week 10, there was statistically significant blinded investigator-rated improvement in skin atrophy (P=0.028) and dullness (P=0.001) for the MEP group over the vehicle group as compared to baseline. The investigator noted MEP induced improvement from baseline at week 14 to include dryness (P<0.001) and laxity (P=0.001), in addition to atrophy (P=0.003) and dullness (P<0.001), as compared to vehicle. The subject data was evaluated by comparing the raw ordinal scores between the MEP and vehicle only group. A statistically significant decrease in skin atrophy (P=0.047) was noted at week 10 with continuing improvement in lines (P=0.014) and atrophy (P=0.020) at week 14 for the MEP over vehicle. These are visual improvements that might be expected after applying a topical soft estrogen

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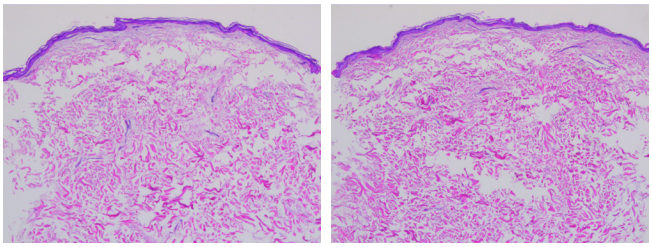
FIGURE 1. Before **(1A)** and after 14 weeks of treatment **(1B)** abdominal tissue H&E images demonstrating a slight increase in dermal collagen.

(1A) **(1B)**



with the length of time required to obtain statistical signficance related to functional skin improvement as compared to cosmetic moisturizer benefit. The percent change differences between baseline and week 14 for MEP versus vehicle are summarized in Table 1.

Five of nine subjects who participated in the biopsy study demonstrated a slight increase in dermal collagen (Figure 1) with four of nine subjects showing an increase in fibroblasts staining positively for estrogen receptors (Figure 2).

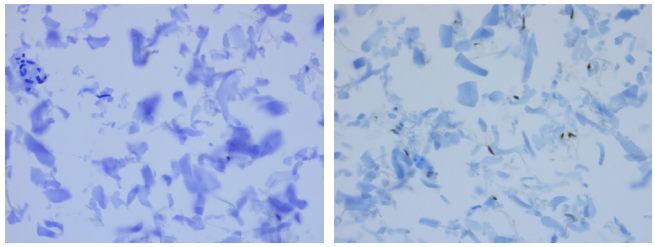
DISCUSSION

This research evaluated the safety and efficacy of MEP in topical formulation applied twice daily in postmenopausal females who had not taken HRT. The safety of topical MEP was demonstrated by the lack of active MEP and the presence of the carboxylic acid MEP inactive metabolite in the serum of subjects who has used the formulation for 12 weeks. This soft effect allowed targeted delivery of the MEP to the skin without systemic side effects, necessary for a cosmeceutical. Restoration of estrogen-like skin effects might induce the production of collagen I, responsible for the strength of the skin, and collagen III, contributing to the elastic skin properties, while reducing the expression of matrixmetalloprotease 1 (MMP-1).[11] The efficacy study carried out for 14 weeks demonstrated a slight increase in collagen from the abdominal biopsies where the MEP was applied twice daily. An increase in fibroblast expressed estrogen receptors was also seen in some subjects as compared to baseline. A more dramatic effect would likely be observed if the study had been carried out longer.

The study was designed to eliminate any moisturizer effect from the vehicle, which can be a confounding variable in cosmeceutical studies. The vehicle in many formulations is responsible for the observed benefits and not the active hero ingredient. This was not the case in this research. Only the MEP could have produced the statistically improved week 14 investigator observations seen in dryness, laxity, atrophy, and dullness over vehicle. The improvement in dryness, usually attributed to the vehicle, may have been due to an improved extracellular matrix with enhanced water holding capabilities from hydrophilic glycosaminoglycans.[12,13] Improvement over vehicle seen by the investigator in laxity and atrophy is consistent with early estrogen-like collagen induced effects. Finally, reduced dullness might have been due to the estrogen-like effect of MEP on the cutaneous microcirculaton.[14] These appearance benefits point to the possible value of MEP as a cosmeceutical ingredient in the treatment of EDS.

FIGURE 2. Before **(2A)** and after 14 weeks of treatment **(2B)** abdominal tissue demonstrating an increase in fibroblast staining for estrogen receptor positivity.

(2A) **(2B)**



Procedures exist for addressing skin surface texture (peels, microdermabrasion, and dermabrasion), facial lines (chemodenervation), and folds (hyaluronic acid fillers), but no current procedures exist for improving the quality of facial skin. If the facial skin could be made more robust, it would drape more artistically over the underlying bones providing a better canvas for other facial rejuvenation procedures. Estrogen deficient skin is thin, fragile, and heals poorly.[14] Microdroplet injection of hyaluronic acid and the use of microneedling or fractionated laser with active ingredients have attempted to improve skin thickness with limited success. Inducing an estrogen-like effect in the skin through use of a cosmeceutical could represent a noninvasive method for improving skin quality and potentially making other cosmetic procedures more effective. Further research is needed with extended subject product use, but MEP appears to be a promising ingredient in estrogen deficient females.

TABLE 1.

Blinded Investigator Assessed Percent Improvement After 14 Weeks Application MEP versus Vehicle		
Visual Criteria Assessment	MEP+Vehicle % Improvement	Vehicle %
Skin Thickness	20%	2%
Fine Lines	8%	2%
Wrinkles	0%	1%
Skin Dryness	54%	16%
Telangiectasias	4%	-3% worsening
Skin Laxity	19%	6%
Skin Atrophy	9%	0%
Skin Dullness	39%	8%
Erythema	11%	0%

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CONCLUSION

This vehicle-controlled double-blinded study demonstrated the safety, tolerability, and efficacy of MEP, a topical soft estrogen cosmeceutical for the treatment of EDS and the improvement of facial appearance without systemic effects. Investigator noted improvements in facial skin dryness, laxity, and dullness and subject noted improvements in facial fine lines and atrophy after 14 weeks of twice daily application are consistent with the histologic observation of increased estrogen receptors. Absent any other known mode of action of MEP, it is presumably the estrogen receptor binding activity of MEP that accounted for these findings. This novel ingredient uniquely addresses appearance issues common in estrogen deficient females.

DISCLOSURES

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