Effects of Topical Copper Tripeptide Complex on CO₂ Laser–Resurfaced Skin

Timothy R. Miller, MD; Jon D. Wagner, MD; Bret R. Baack, MD; Karl J. Eisbach, MD

Objective: To evaluate the role of skin care products that contain a copper tripeptide complex, glycyl-L-histidyl-L-lysine-Cu²⁺ (GHK-Cu), in treating carbon dioxide (CO₂) laser–resurfaced skin.

Methods: Patients meeting the inclusion criteria underwent circumoral skin resurfacing using a CO₂ laser at standard settings. Patients were then randomized to receive post-treatment skin regimens with or without GHK-Cu. Evaluations for erythema throughout the posttreatment period were performed using computer software and blinded evaluators. In addition, overall improvement in wrinkles and overall improvement in skin appearance 12 weeks after treatment were assessed. Patients completed a validated questionnaire before and 12 weeks after treatment.

Results: Thirteen patients completed the study. Computer analysis and blinded evaluators found no statistically significant differences between groups for earlier resolution of erythema. All the patients experienced significant improvement in wrinkles and overall skin quality, but no differences were found between groups. The results of the questionnaire indicated a significant difference in the posttreatment improvement of overall skin quality for patients using GHK-Cu (P = .04).

Conclusions: Copper tripeptide complex (GHK-Cu) skin care products placed on CO₂ laser–resurfaced skin offered no significant reduction or resolution of posttreatment erythema. Objective evaluation found no significant improvement in wrinkles or overall skin quality. However, patient satisfaction was significantly higher for those who used GHK-Cu skin care products after CO₂ laser skin resurfacing.

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ydroliclyl-L-histidyl-L-lysine-Cu²⁺ (GHK-Cu) is a copper tripeptide complex that has recently been introduced into skin care products. Interest in including GHK-Cu in skin care products has arisen from the results of earlier research. Glycyl-L-histidyl-L-lysine is a naturally occurring tripeptide originally isolated in the early 1970s from human plasma. It has a high affinity for copper and readily forms a copper tripeptide complex, GHK-Cu. Initial laboratory studies with GHK-Cu showed positive wound-healing properties. The effects on wound healing were numerous and include the stimulation of collagen synthesis, angiogenesis, and the modulated expression of glycoaminoglycans, proteoglycans, and metalloproteinases. In vivo studies involving animal models reinforced the laboratory findings and reported accelerated wound-healing rates and favorable wound-contraction properties. These wound-healing characteristics of GHK-Cu were further tested in clinical trials on diabetic ulcers and on Mohs surgical wounds, and were found to significantly improve reepithelialization and overall wound healing. These favorable wound-healing results attributed to GHK-Cu may have potential benefits for the patients of facial plastic surgeons.

The wound created by the carbon dioxide (CO₂) laser requires a lengthy recovery period and is fettered by prolonged posttreatment erythema. Despite numerous studies offering support for nonablative techniques for skin rejuvenation, many facial plastic surgeons still support use of the CO₂ laser for more advanced photoaged skin. Consequently, a posttreatment strategy that could hasten the recovery period would be beneficial.

Current posttreatment routines include semiocclusive sheeting and applications of various skin care products. Semiocclusive sheeting works well, but around the perioral area it is often displaced and, therefore, provides inconsistent coverage. Most skin care products are petrolatum based and may be enriched with vitamins, minerals, or organic substances to aid healing. However, unique to the copper tripeptide complex is the cumulative evidence of its potential to facilitate the

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wound-healing process. Therefore, we sought to objectively evaluate the effects of GHK-Cu–containing skin care products on wound healing by following a cohort of patients through CO2 laser treatment.

METHODS

All the patients who met the criteria for circumoral laser resurfacing from August 2004 to February 2005 were evaluated for inclusion in the study. Inclusion criteria were Fitzpatrick skin types I and II and having the ability to adhere to and perform the postoperative skin care regimen, which included frequent follow-up clinical evaluations. Patients undergoing full-face laser treatments were excluded because the skin of these patients is covered with semioptic sheathing in the postoperative period. In addition, patients undergoing lip augmentation or those with recent use of fillers around the perioral area (eg, lips and nasolabial folds) were excluded. After providing informed consent, all the patients underwent identical CO2 circumoral laser treatments (Ultrapulse 3000C; Coherent Inc, Santa Clara, Calif). The laser was set to 300 mJ/pulse, 60 W, and 3 passes were performed. All the passes used a computer-generated rectangular pattern set to 5. The size and density levels changed accordingly (first pass: size 9, density 6; second pass: size 9, density 3; and third pass: size 8, density 4).

After treatment, the patients were randomized into 1 of 2 groups. Group A used a petrolatum-based product (Biomedical Gentle Healing Ointment; LaRoche-Posay, New York, NY) until reepithelialization, followed by the daily use of skin moisturizers (Toleriane, Tolerin, and Hydraphase; LaRoche-Posay). Group B used a petrolatum-based product containing GHK-Cu (Complex Cu3 Intensive Tissue Repair Crème; ProCyte Corp, Redmond, Wash) until reepithelialization, followed by the daily use of skin-moisturizing products that also contained GHK-Cu (Complex Cu3 Post-Laser Lotion and Neova therapy skin care products [Day Therapy SPF 20, Night Therapy, and Crème De La Copper]; ProCyte Corp).

Both groups received the same postoperative skin care instructions, which included the liberal application of skin care products in the immediate postoperative period, in association with frequent cleansing of the treated area. After reepithelialization, maintenance skin care included the daily use of sunscreens and frequent application of the skin moisturizers listed in the previous paragraph. The regimen was followed for 12 weeks because our intent was to inundate the healing tissues of group B with the GHK-Cu complex during an extended period.

The patients had postoperative follow-up evaluations on day 3 and at 1, 2, 6, and 12 weeks. During the postoperative period, no patients were provided with hydroquinone or corticosteroid creams.

PHOTOGRAPHY

All the patients had standardized digital photographs taken preoperatively, on postoperative day 3, and at 1, 2, 6, and 12 weeks postoperation. Photography sessions were conducted makeup free in a windowless room with standardized lighting. Digital photographs were captured using a Nikon camera (D70 SLR; Nikon Inc, Melville, NY), positioned on a tripod at a fixed distance and a set focal length. The digital camera was manually white balanced to avoid the potential color aberrations associated with the auto–white balance feature. In addition, all the photographs contained a ColorChecker Color Rendition Chart (GretagMachbeth LLC, New Windsor, NY) held by the patient in repose to further standardize the images during computer processing (Figure 1). To further reduce in-camera processing that might affect color acquisition from one image to the next, images were captured using the custom setting in the image enhancement mode. This way, features such as sharpening, contrast, color reproduction, saturation, and hue were set to be identical from one photograph to the next. Furthermore, the images were captured in the raw (Nikon Electronic Format) file format option to reduce the potential loss of information and quality attained by saving images to JPEG file formats.

QUANTITATIVE COLOR ANALYSIS

Because prolonged postoperative erythema can be significant after CO2 laser skin resurfacing, we sought to determine whether skin products containing GHK-Cu, with its purported wound-healing capabilities, would hasten the resolution or alter the degree of postoperative erythema. Image-editing software (Photoshop CS; Adobe Systems Inc, San Jose, Calif) was used to perform quantitative analysis of the color changes in the treated areas throughout the postoperative recovery period. This mode of color analysis through digital photography has been found to be reliable in recent studies.

In brief, the colors seen through our eyes and processed through a digital camera are representations of the RGB (red, green, blue) color model. Various combinations of these 3 primary colors of light form other colors that we interpret. For example, white light represents the maximal intensity of all 3 colors, whereas black represents the absence of all 3 colors. An equal blend of all 3 colors results in a natural midtone color (eg, gray), and various combinations form the other colors that we observe. We used these concepts to analyze color changes in the patients.

Digital images were transferred to a laptop computer (Pavilion zv5000; Hewlett-Packard Co, Palo Alto, Calif) through a USB (universal serial bus) 2.0 connection with the camera. Before color analysis, the ColorChecker Color Rendition Chart was used to standardize the tonal range of the images: shadows, highlights, and midtones. In addition, Photoshop CS color schemes were calibrated with the computer’s monitor using Photoshop CS software instructions. Moreover, customized preferences were established. For example, the working space, which defines color presentation and consistency on opening images, was defaulted to Adobe RGB (1998), and the cache feature for rendering histogram analysis was turned off. All these steps, combined with proper white balancing, are essential to reproduce the actual colors represented on the image (patient) and to accurately duplicate colors from one image to the next.
The images were opened in Photoshop CS and magnified to 100%. Before the study, the focal length and the camera-to-patient distance were defined so that only the perioral area would be displayed on magnification to 100%. In Photoshop CS, the image mode was set to RGB color and 16 bit/channel. Two areas on all the images were evaluated: the upper lip and the lower lip and mentum. The rectangular marquee function was used to capture an area totaling 100,000 pixels (Figure 2).

Histogram pixel analysis of red, blue, and green was then undertaken. Means (standard deviations) were acquired from the gaussian distribution.

On histogram analysis, the mean values from only the red pixels are not enough to accurately determine redness (erythema) on an image because the values calculated for red pixels can be similar in an individual with Fitzpatrick skin type I and an object that is considered a standard hue of red (Table 1).

To determine the degree of redness, an erythema index (EI) must be applied.

Setaro and Sparavigna calculated an EI by subtracting the mean red pixel values from the mean green pixel values (EI = red – green). They proposed that erythema arises from increased blood flow, which introduces more erythrocytes into a specific site. Erythrocytes are largely composed of hemoglobin, which absorbs green light, thereby reflecting the color red. However, this formula for an EI is insufficient for 2 reasons. First, from color theory, light that is absorbed (or subtracted) will reflect its complementary color. The reflective or complementary color of green light is magenta, not red (Figure 3). In addition, hemoglobin absorbs both green and blue light (Figure 4).

From color theory, a mixture (or absorption) of 2 colors will create either a primary (red, blue, green) or a secondary (cyan, magenta, yellow) color. All secondary colors reflect a primary color. For example, green and blue will create cyan, a secondary color. The importance of the color cyan is that its reflective or complementary color is red. Therefore, the more cyan (green and blue) that is absorbed, the more red (erythema) that is reflected by the subject of interest.

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Table 1. Comparison of Redness and Mean Pixel Values From RGB Histogram Analysis

<table>
<thead>
<tr>
<th>Sources for Comparison</th>
<th>Red</th>
<th>Green</th>
<th>Blue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red color standard*</td>
<td>164</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>Carbon dioxide laser–treated skin (2 wk)</td>
<td>153</td>
<td>102</td>
<td>89</td>
</tr>
<tr>
<td>White skin (Fitzpatrick type I)</td>
<td>164</td>
<td>132</td>
<td>110</td>
</tr>
</tbody>
</table>

Legend: R, red; G, green; B, blue; M, magenta.

*ColorChecker Color Rendition Chart (GretagMacbeth LLC, New Windsor, NY).

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EI results during the study were compared separately for each group using a matched repeated-measures analysis of variance (rmANOVA). With significant difference, posttesting was applied. The reason for this analysis was to determine the length of time it took each group to return to preoperative skin tones according to the EI. In addition, each period was examined using an unpaired t test to determine differences between the groups. In this study, the analysis was used to determine whether one group’s EI was more intense than that of the other at specific times. Because of the large sample of pixels tested [ie, 100,000] and the gaussian distribution of values, parametric statistical tests were performed on all data derived from computer analysis; otherwise, nonparametric tests were applied secondary to the small study sample.) The reliability of the protocol was tested before the study. Three nontreated individuals ( Fitzpatrick skin types I, II, and IV) were photographed on 3 different occasions. Histogram analysis was then performed on the series of images for each individual. A matched rmANOVA statistical test was then performed for each individual’s series. No statistical differences were found from one photography session to the next, confirming the reproducibility of our image acquisition techniques. Further statistical analysis revealed significant differences between the Fitzpatrick types I and IV skin tones (RGB: P<0.05; Mann-Whitney test), establishing sensitivity of the histogram color analysis.

QUALITATIVE ANALYSIS

Two blinded board-certified plastic surgeons critically analyzed the digital images. The criteria evaluated were postoperative erythema, rhytides, and overall improvement. Images were viewed and evaluated on the same monitor as previously stated and in similar lighting conditions. Printed materials and different computer monitors were not used to avoid errors in color reproductions. The evaluations were performed in the following order.

Erythema was evaluated by presentation of all the images in random order. The evaluators were blinded to the treatment arm and the postoperative length of time since laser treatment. Erythema was assessed on a 4-point scale (0=no erythema; 1=slight erythema, not well-demarcated margins; 2=moderate erythema, well-demarcated margins; and 3=intense erythema, raised margins). The values were averaged (median) between the 2 evaluators, and statistical analysis was performed. Similar to the pixel analysis described previously in this article, each group’s EI was examined throughout the postoperative period using a matched rmANOVA. With significant difference, posttesting was applied. Further analysis evaluated the differences between the groups at specific periods using the Mann-Whitney test.

Rhytides were then assessed by evaluating postoperative and 12-week postoperative photographs placed in random order. The evaluators were blinded to the treatment arm and to the postoperative and preoperative status. Determination of rhytides was performed using the 9-point Fitzpatrick wrinkle classification. Comparisons of preoperative and 12-week postoperative scores were subsequently performed in each group using a Wilcoxon matched pairs test. A Mann-Whitney test was used to examine the preoperative vs 12-week postoperative differences in groups A and B.

To assess overall improvement, preoperative and 12-week postoperative images were analyzed simultaneously. A 5-point grading scale was used to assess improvement (0=none, 1=acceptable, 2=good, 3=very good, and 4=substantial). The scores between the evaluators were averaged (median), and statistical analysis evaluated overall improvement in each group (Wilcoxon test) and between the groups (Mann-Whitney test).

SUBJECTIVE ANALYSIS

The validated Skin Rejuvenation Outcomes Evaluation (SROE) patient questionnaires were completed preoperatively and 12 weeks postoperatively. Statistical analysis using a Wilcoxon matched pairs test was applied to each group to determine differences between preoperative and postoperative results. In addition, differences between groups A and B were assessed by means of a Mann-Whitney test. All statistical analyses were performed using StatMate and Instat 3.06 (GraphPad Software, San Diego, Calif); P<0.05 (2-tailed) was considered statistically significant.

RESULTS

Twenty patients were evaluated. Six prospective patients were not included because of their inability to return for postoperative evaluations and photography or because they were undergoing perioral augmentation. Fourteen patients were enrolled in the study. One patient was excluded from group B (the GHK-Cu cohort) for self-admitted infrequent use of the products. Therefore, 13 patients (6 in group A and 7 in group B) completed all aspects of the study. Group A included 1 patient considered to have Fitzpatrick skin type I; the remaining patients, including group B patients, had Fitzpatrick skin type II. The age range for group A was 61 to 70 years and for group B was 50 to 77 years. A Mann-Whitney test revealed no statistically significant age difference between the randomized groups. There were no adverse reactions or infections in either group.

ERYTHEMA ANALYSIS

The data provided by histogram analysis were used to calculate the EI. Data from postoperative day 3 were excluded because 9 (69%) of the 13 patients had exudates or crusting covering more than 50% of the perioral area, precluding an accurate analysis. Statistical analysis revealed significant differences in the EI throughout the postoperative period for both groups (rmANOVA: P<0.001 for each group). Posttesting identified the differences between preoperative values and postoperative day 7 values (P<0.001 for each group), 2-week values (group A: P<0.001; group B: P<0.05), and 6-week values (group A: P<0.01; group B: P<0.05). No statistically significant differences were found between preoperative and 12-week postoperative values for group A or B (Table 2 and Figure 5). Each period was examined separately for differences in the EI scores between the 2 groups. No statistically significant differences were found.

Owing to the results and the small sample size, a power statistical analysis was performed in an attempt to reduce the possibility of a type II statistical error. For group A, the mean±SD difference between the preoperative and the 12-week postoperative periods was 9±11. Group B had a mean±SD difference of 4±10. Using these values, the study had 80% power to detect a difference between means of 12 with a significance level of .05. The ability to detect a difference of 12 is important because, in either group, a mean difference of 12 or higher found statistically significant differences when preoperative values were compared with any postoperative values.
Table 2. Computer Analysis of the Erythema Index: Comparison of Preoperative and Postoperative Values*

<table>
<thead>
<tr>
<th>Group</th>
<th>7 d Postop</th>
<th>2 wk Postop</th>
<th>6 wk Postop</th>
<th>12 wk Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.01</td>
<td>NS</td>
</tr>
<tr>
<td>Group B</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: NS, not significant; postop, postoperative; preop, preoperative.
*Data are presented as P values. See the “Methods” section for definitions of the groups.

Figure 5. Computer analysis of the erythema index. See the “Methods” section for definitions of the groups.

Two plastic surgeons (J.D.W. and B.R.B.) scored erythema on a 4-point scale. Of the 78 observations, there was complete agreement on 59 (76%); the remaining observations were within 1 point. Analysis revealed statistical differences (nonparametric rmANOVA: \( P < .001 \) for each group). Posttesting produced differences between preoperative and postoperative day 7 (group A: \( P < .01 \); group B: \( P < .001 \)) and 2-week (group A: \( P < .05 \); group B: \( P < .01 \)) values. No statistical differences were seen at 6 and 12 weeks for either group (Table 3 and Figure 6). Statistical analysis between groups A and B at all preoperative and postoperative points identified no significant differences.

RHYTIDE ANALYSIS

Rhytides were evaluated using a 9-point grading scale. Assessments were performed, and the observations were either exact (75%; 21/28) or within 1 point on all evaluations. Most patients were assessed as having Fitzpatrick wrinkle class II or III. Three patients in group B were categorized into Fitzpatrick class I wrinkles. Not enough data points were available to reach statistical significance, but a trend toward a larger difference (more improvement) was calculated for group B (Table 5).

OVERALL IMPROVEMENT

Overall improvement was scored on a 5-point scale to determine the quality of the improvement. Factors affecting preoperative vs postoperative scores included improvement in rhytides, skin texture, and in quality, color, and appearance. The evaluators were in complete agreement on 11 (79%) of the 14 evaluations, and the remaining scores were within 1 point.

The distributions of overall improvement are listed in Table 6. There was no significant difference in overall improvement between groups A and B (\( P = .56 \)). A statistical analysis that excluded patients with Fitzpatrick class I wrinkles was performed, but not enough data points were available to reach statistical significance. However, all the patients in group B categorized into Fitzpatrick wrinkle class II or III had substantial overall improvement.

SUBJECTIVE QUESTIONNAIRE

A validated questionnaire (SROE) was completed by all the participants. Statistical analysis of preoperative to 12-week postoperative scores found significant differences in both groups (Table 7). The differences between the 2 groups were then compared, and a significant difference was calculated (\( P = .04 \)), with group B having a larger difference between preoperative and 12-week postoperative scores. There was no significant difference between group A and B preoperative scores (\( P = .99 \)).

The copper tripeptide complex (GHK-Cu) was examined in this present study to determine its clinical usefulness for patients undergoing facial plastic surgery. Previous studies included laboratory examinations that confirmed the ability of GHK-Cu to modulate the expression of factors required for wound healing. For example, Pollard et al6 examined GHK-Cu on normal and irradiated fibroblasts and found accelerated population-doubling times in both groups and increased growth factor production in irradiated fibroblasts compared with controls. Simeon et al7 used an animal model and found that the introduction of GHK-Cu increased cell invasion and extracellular matrix deposition and, later in the healing phase, modulated the expression of metallopro...
teinases, thereby affecting wound remodeling and angiogenesis. In clinical studies, Mulder et al. performed a randomized, evaluator-blinded, placebo-controlled study of diabetic patients with plantar ulcers. Treatment with GHK-Cu significantly improved the percentage of closure and increased the rate of closure by a factor of 3.11 The favorable effects of GHK-Cu reported by these and other studies would be beneficial to patients undergoing skin-resurfacing treatments. To assess the ability of GHK-Cu to improve wound healing, the present study evaluated patients receiving circumoral CO2 laser-resurfacing treatments. This mode of treatment, in contrast to dermabrasion and chemical peels, can deliver a more consistent depth of dermal injury from one patient to the next, when the application is based on standardized settings. To further minimize variability, only patients with Fitzpatrick skin types I and II were included in the study to reduce the potential of postoperative pigmentation problems confounding the results.

The study used 2 measures to determine the presence of erythema. The use of computer analysis for color measurements has been described, but its use in facial plastic surgery studies is lacking. The benefits of quantitative analysis in color measurements are more consistent, reproducible results and the further limitation of bias. The quantitative results in the present study demonstrate that groups A and B had significant differences.

### Table 3. Evaluator-Blinded Erythema Scores: Comparison of Preoperative and Postoperative Values*

<table>
<thead>
<tr>
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</tr>
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<td>&lt;.001</td>
<td>&lt;.01</td>
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### Table 4. Fitzpatrick Wrinkle Scale: Distribution of Patient Assessments

<table>
<thead>
<tr>
<th>Class</th>
<th>Score</th>
<th>Wrinkling</th>
<th>Patients, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1-3</td>
<td>Fine</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>4-6</td>
<td>Fine to moderate depth, moderate number of lines</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>7-9</td>
<td>Fine to deep, numerous lines</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table 5. Fitzpatrick Wrinkle Scores (9-Point Scale): Assessment of Preoperative and 12-Week Postoperative Improvement*

<table>
<thead>
<tr>
<th>Group</th>
<th>Preop</th>
<th>12 wk Postop</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A†</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>6.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Group B‡</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>2.5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>6.5</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: postop, postoperative; preop, preoperative.

†In group A, the mean improvement was 2.4 and the median improvement was 1.75.
‡In group B, the mean improvement was 2.0 and the median improvement was 2.0. Including Fitzpatrick classes II and III only (excluding Fitzpatrick class I), the mean improvement was 3.25 and the median improvement was 3.25.

### Table 6. Stratification of Overall Improvement Scores*

<table>
<thead>
<tr>
<th>Overall Improvement</th>
<th>Patients, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Group A: 0</td>
</tr>
<tr>
<td>Acceptable</td>
<td>0</td>
</tr>
<tr>
<td>Good</td>
<td>1</td>
</tr>
<tr>
<td>Very good</td>
<td>4</td>
</tr>
<tr>
<td>Substantial</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
</tr>
</tbody>
</table>

*See the “Methods” section for definitions of the groups.

†Fitzpatrick wrinkle class I.
in the EI between preoperative and postoperative day 7 and at 2 and 6 weeks. By 12 weeks, there were no statistically significant differences. In addition, there were no statistically significant differences between the groups in terms of erythema intensity at any time measured.

The data indicate that some time after 6 weeks and no later than 3 months, both patient populations returned to preoperative skin tone hues (Figure 5 and Figure 6). In addition, the data demonstrate that the EI peaks at 1 week and then begins to diminish significantly during the following weeks. No measurements were obtained between the 6- and 12-week periods, which is a limitation of the study. A potential difference in this period would have significant relevance for patients concerned with postoperative erythema. Future studies may investigate this period to determine whether significant differences exist.

The EI used in the present study was a modification of an index used in a previous study. The index is a simple formula based on the absorption characteristics of hemoglobin. The current EI considers the absorption of blue and green light equally. Although hemoglobin absorbs blue and green wavelengths, it may do so at differing ratios. Therefore, more sophisticated mathematical formulas, which also consider the absorption properties of the extracellular matrix and other relevant substances throughout the healing process, may theoretically provide more accurate measurements.

The masked observations of erythema by 2 physicians (J.D.W. and B.R.B.) closely follow the quantitative (computer) results. The levels similarly peaked at 1 week but returned to preoperative levels after 2 weeks but before 6 weeks, sooner than the quantitative results. The difference may be secondary to the grading scale used by the evaluators. Part of the definition of erythema relied on demarcated borders surrounding the erythema, the absence of which would direct the evaluator to a lower score despite visualizing substantial erythema. Furthermore, additional categories or a broader scale to interpret erythema may have added more sensitivity to the evaluations and perhaps results more similar to the computer analysis.

The evaluation of rhytides arises from the results of laboratory data suggesting that GHK-Cu has a significant effect on collagen production and tissue remodeling. In addition, abstracts have been presented at meetings reporting the data of clinical studies using GHK-Cu skin care products. The studies have shown significant improvements in the appearance of photoaged skin. In contrast, the present study presents no statistically significant results to support the ability of GHK-Cu to independently improve rhytides. However, this study was based on laser-resurfaced skin, whose treatment is well known to improve rhytides. Consequently, the effects of GHK-Cu may be confounded in this situation compared with its application on untreated photoaged skin.

Although no statistically significant differences were calculated between the groups, a perceptible improvement was seen in the cohort using GHK-Cu products. These improvements were seen in patients with higher Fitzpatrick wrinkle class scores (II and III). The range of improvement, as assessed by differences between preoperative and postoperative wrinkle scores, showed a trend toward superior improvement for group B patients (Table 5). Future studies that examine a larger subset of patients for a longer period may find a significant benefit.

The overall improvement evaluation assessed erythema and rhytides, in addition to other qualities, such as skin texture, quality, pigmentation, and appearance. Both groups had most of their outcomes scored in the higher categories (ie, substantial or very good), and statistical analysis showed no significant differences when both groups were compared. Of interest was the subset of patients with substantial improvements. All the patients using GHK-Cu classified into the higher Fitzpatrick wrinkle classes (II and III) had overall improvements rated as substantial: the highest category score. In contrast, of 6 patients in group A with similar Fitzpatrick wrinkle scores, only 1 had improvements scored in this category. These results suggest the need for future studies to evaluate these findings in a larger cohort of patients.

Alsarraf developed validated quality-of-life instruments, including one specifically designed to encompass skin rejuvenation procedures. The SROE provides a quantitative measurement to assess patient satisfaction that not only is based on physical change and appearance but also includes emotional and social acceptance components. The evaluation was important to include in the study because the other measures were based on isolated assessments, which may not consider all variables essential to an excellent outcome. The results of the questionnaire determined that the GHK-Cu group had significantly more personal satisfaction with their results at 3 months than patients in group A. The results are not entirely void of bias. Patients in group B (the GHK-Cu group) received more products and required relatively more patient-physician interaction for product education and instructions for postoperative timing and sequence of product application. In addition, the products were free of charge and open label; therefore,

<table>
<thead>
<tr>
<th>Table 7. Validated SROE Patient Questionnaire Scores*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score, Median (IQR)</strong></td>
</tr>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Group A</td>
</tr>
<tr>
<td>Group B</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; postop, postoperative; preop, preoperative; and SROE, Skin Rejuvenation Outcomes Evaluation.

*See the “Methods” section for definitions of the groups.
the potential for reporting bias (ie, the desire to please or thank the physician) should be considered.

In conclusion, the use of a copper tripeptide complex, GHK-Cu, on CO2 laser–resurfaced skin offered no statistically significant reduction in the intensity or duration of postoperative erythema. However, patient satisfaction was significantly higher when GHK-Cu was applied. The data suggest that copper tripeptide complexes may provide a superior overall result and improvement in preoperative vs postoperative wrinkle scores in Fitzpatrick wrinkle classes II and III; however, larger studies are required to confirm these data.

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REFERENCES