Clinical Improvement of Photoaged Skin with 50% Glycolic Acid

A Double-Blind Vehicle-controlled Study

NATHAN NEWMAN, MD • ARMAND NEWMAN, MD
LAWRENCE S. MOY, MD • REZA BABAPOUR, MD
ALAN G. HARRIS, MD • RONALD L. MOY, MD

BACKGROUND. Although there is increasing interest in the use of glycolic acid in the treatment of photoaged skin, to our knowledge, no controlled study has been done to assess the efficacy or the mode of this agent.

OBJECTIVE. The purpose of this study was to determine whether 50% glycolic acid can improve photoaged skin and to study the histological basis for this improvement.

METHODS. Forty-one volunteers were recruited into this double-blind vehicle-controlled study. Glycolic acid (50%) or vehicle was applied topically for 5 minutes to one side of the face, forearms, and hands, once weekly for 4 weeks. Punch biopsies were taken at pretherapy and at 5 weeks for histologic study.

RESULTS. Significant improvement noted included decrease in rough texture and fine wrinkling, fewer solar keratoses, and a slight lightening of solar lentigines. Histology showed thinning of the stratum corneum, granular layer enhancement, and epidermal thickening. Some specimens showed an increase in collagen thickness in the dermis.

CONCLUSION. The results of this study demonstrate that the application of 50% glycolic acid peels improves mild photoaging of the skin.


Photoaging refers to skin changes or skin damage that is caused by prolonged exposure to ultraviolet light. The damaging effects of ultraviolet exposure are responsible for the effects of premature aging of the skin, thus resulting in rough texture, wrinkling, and the formation of solar keratoses and solar lentigines. In addition to the loss of elasticity and the more serious consequences of skin malignancies. Recently, interest has centered on chemical agents such as retinoic acid (tretinoin), isotretinoin, trichloracetic acid, and phenol as treatments of photoaged skin.

However, today the focus has been shifted to glycolic acid, a mild chemical peeling agent. Glycolic acid is an alpha hydroxy acid (AHA). AHAs, such as glycolic, lactic, and citric acids, are naturally occurring acids that are found in many different food types. Glycolic acid is present in sugar cane, while lactic acid is found in sour milk. Glycolic acid has been reported to cause epidermolysis when applied to the skin for 3-7 minutes, depending on skin type, thickness of stratum corneum, and the concentration of the glycolic acid. The noticeable effects on the epidermis have resulted in its increased popularity as a superficial chemical peeling agent.

In this study the clinical improvements in photoaged skin treated with 50% glycolic acid peels have been correlated with histological data in an attempt to study the basis for these clinical changes. To our knowledge, this paper represents the first clinical double-blind vehicle-controlled study of 50% glycolic acid peels on photoaged skin.
Materials and Methods

Patient Selection and Instruction
Forty-one volunteers (9 male, 32 female) with a mean age of 59 years, ranging from 35 to 70 years, clinically diagnosed with photoaged skin (see Clinical Evaluation for definition) of the face, dorsal forearms, and hands, who were otherwise healthy, were recruited into the study. Individuals with a history of tretinoin use, radiation dermatitis, dermabrasion, chemical peels, eczema, psoriasis, or other forms of dermatitis were excluded from the study. All topical medications were stopped 2 weeks prior to the study. Patients were instructed to continue to use the same brand and quantity of make-up during the study as before. Patients were provided with a mild soap and a moisturizer that did not contain AHAs or sunblocking agents, and were asked to use only these products for the duration of the study. Informed consent was obtained from all volunteers who were accepted into the study. Patients were evaluated and standardized views of the study areas were photographed without the use of cosmetics before treatment and at 5 weeks.

Treatment Regimen
Study areas consisted of dorsal aspects of forearms, dorsum hands, and face. Tube A (50% glycolic acid gel) was assigned to each patient's left side, and tube B (vehicle gel) was assigned to each patient's right side. Tube A contained 50% glycolic acid solution, dissolved in water, plus a special mild thickening agent, which was added to achieve the proper consistency. The 50% glycolic acid gel in tube A was of pharmaceutical grade, unbuffered, not neutralized, with a pH of 1.2. The double-blind study was designed so that neither the patients nor the dermatologists knew the contents of either tube A or B.

First, the study areas were degreased using alcohol. Second, all patients were treated with a premeasured amount of gel (1 ml) from each tube, which was applied to the assigned side of the body areas used in the study. The gels were applied evenly using a new cotton ball for each site. Then, the gels were washed off with water using a fresh towelette for each half of the body. Extreme care was used, during the application and removal of the gels, to prevent cross-contamination. Patients were treated with the gels once every 7 days for 4 consecutive weeks. Punch biopsies (3.5 mm) were taken from both treated and control areas at pretreatment and at 5 weeks, ie, 1 week after the last application of glycolic acid or vehicle. These biopsy specimens were processed for light microscopic comparative evaluations.

Clinical Evaluation
The study areas were evaluated at pretherapy and at 5 weeks by one of the dermatologists who did not apply the gels. The study areas were graded according to five clinical parameters of photoaged skin: 1) rough texture defined as a uneven appearance with uneven surface changes; 2) solar keratoses defined as diffuse erythema with keratotic adherent scaling; 3) solar lentigines defined as dark brown macules with distinct borders measuring between 3 and 6 mm; 4) fine wrinkling measured as less than 1 mm in width and depth; and 5) course wrinkling measured as a width and depth greater than 1 mm and presence of cross-wrinkling. An overall rating of mild, moderate, and severe for each area under observation was conducted by one of the nontreating dermatologist. Lesion counts were performed for solar keratoses and solar lentigines. At each weekly visit, the nontreating dermatologist graded the study areas for overall improvement. The grading scale ranged from -1 to + 3 ( - 1 = worse, 0 = no change, + 1 = mild improvement, +2 = moderate improvement, and +3 = much improvement).

Light Microscopy
At pretreatment, punch biopsy (3.5 mm) specimens were taken from the proximal third of each dorsal forearm 5 cm from the antecubital fossa. At 5 weeks, a second punch biopsy (3.5 mm) was taken 1-2 cm away from the previous biopsy site. Biopsy specimens were fixed in 10% neutral-buffered formalin and processed through paraffin sections for light microscopy. These sections were stained with hematoxylin and eosin. Two dermatopathologists, who were blinded to the assignments, evaluated these biopsy sections. Quantitative measurements of biopsy specimens were made using a calibrated optical micrometer. Seven adjacent high power fields were used per section to measure the stratum corneum, the stratum granulosum, and the epidermal thickness.

Statistical Analysis
The results of the study were assessed using the chi square test and considered statistically significant when P < .05 for the two-tailed test.
Results

Clinical Evaluation

Only 34 patients completed the study. Seven patients dropped out of the study because they missed their weekly treatment visit. Clinical data are summarized in Tables 1-3. At the fifth week of evaluation, statistically significant ($P < .0001$) improvement in rough texture (Table 1) was observed in 91%, 88%, and 91% of the 34 patients treated with 50% glycolic acid versus 3%, 0%, and 3% of those treated with the vehicle-control on the hands, forearms, and face, respectively. The number of solar keratoses (Table 2) was decreased, with a statistical significance of ($P < .0001$) in 27% on the hands, 36% on the forearms, and 30% on the face of the 34 patients treated with 50% glycolic acid as compared with no improvement in any of the controls.

<table>
<thead>
<tr>
<th>Table 1. Evaluation of Rough Texture in 50% Glycolic Acid (GA)- and Vehicle (V)-treated Skin at 5 Weeks in 34 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Much Improved</td>
</tr>
<tr>
<td>Improved</td>
</tr>
<tr>
<td>Slightly Improved</td>
</tr>
<tr>
<td>No Change/Worse</td>
</tr>
</tbody>
</table>

This table demonstrates the results of rough texture improvement after the series of four weekly 50% glycolic acid treatments. The evaluations were performed by a blinded dermatologist, before and after the treatment regimen. The areas treated with 50% glycolic acid showed a statistically significant improvement of 91%, 88%, and 91%, respectively, on the hand, forearm, and face over the control ($P < .0001$).

<table>
<thead>
<tr>
<th>Table 2. Evaluation of Solar Keratosis in 50% Glycolic Acid (GA)- and Vehicle (V)-treated Skin at 5 Weeks in 34 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Much Improved</td>
</tr>
<tr>
<td>Improved</td>
</tr>
<tr>
<td>Slightly Improved</td>
</tr>
<tr>
<td>No Change/Worse</td>
</tr>
</tbody>
</table>

The areas treated with 50% glycolic acid showed a statistically significant decrease in solar keratosis of 27%, 36%, and 30% on the hand, forearm, and face, respectively, over the control ($P < .01$).

Fine wrinkling (Table 3) of the face was statistically significantly improved ($P < .0001$) in 85% of the 34 study patients on the side treated with 50% glycolic acid as compared with 0% on the vehicle-controlled side (Figure 1). Course wrinkling was not improved on any of the sites in any of the 34 patients. Solar lentigines were slightly lighter in color on the areas treated with 50% glycolic acid, when compared with the controls (Figure 2).

<table>
<thead>
<tr>
<th>Table 3. Evaluation of Fine Wrinkling in 50% Glycolic Acid (GA)- and Vehicle (V)-treated Skin at 5 Weeks in 34 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Much Improved</td>
</tr>
<tr>
<td>Improved</td>
</tr>
<tr>
<td>Slightly Improved</td>
</tr>
<tr>
<td>No Change/Worse</td>
</tr>
</tbody>
</table>

The facial areas treated with 50% glycolic acid showed a statistically significant improvement of 85% over the control ($P < .0001$).
Figure 1. A) Before and B) 5 weeks after treatment of fine wrinkling on the face of a 65-year-old woman with four weekly treatments of 50% glycolic acid showing a decrease in fine wrinkling.

Figure 2. A) Before and B) 5 weeks after treatment of solar keratosis and rough texture on the forearm of a 69 year-old man with four weekly treatments of 50% glycolic acid. There is a decrease in the number of solar keratosis with smoother skin texture.

The adverse effects noted included erythema, scaling, and irritant dermatitis. At each visit patients reported a mild stinging sensation during the application of the 50% glycolic acid peel. However, patients experienced minimal discomfort and tolerated the 50% glycolic acid treatments well. At the 5-week evaluation time, no post-peel erythema or scaling was noted. Significantly, no scarring, hyper- or hypo-pigmentation, or persistent erythema was seen in any of the 34 patients in the study.

Light Microscopy
Histologic evaluation showed a 53% decrease in the stratum corneum layer treated with 50% glycolic acid, whereas the vehicle-treated stratum remained unchanged. This 53% decrease reflects the compaction of the basket-weaved stratum corneum after treatment with glycolic acid (Figure 3). There was also a 19% increase in the epidermal thickness, and a 50% increase in the layer thickness as well as increase in the number of granules of the stratum granulosum. There was no change in the thickness of the epidermis in the vehicle-treated areas. In some of the biopsy specimens, there appeared to be some increase in collagen thickness and prominence, as seen in Figure 4.
Figure 3. Light micrograph of paraffin sections stained with hematoxylin and eosin from the proximal forearm of A) pretreated and B) 5 weeks after treatment with four weekly applications of 50% glycolic acid showing compaction of the stratum corneum (thin arrow), enhancement of the granular layer (thick arrow), and an increase in the epidermal thickness (X400).

Figure 4. A) Light micrograph of paraffin sections stained with hematoxylin and eosin from the proximal forearm showing a basket-weave pattern of the pretreated stratum corneum. B) At 5 weeks, there is compaction of the stratum corneum, increase in the granular layer, and an increase in the epidermal thickness after four weekly treatments with 50% glycolic acid. In this micrograph specimen there appears to be a decrease in melanin content in the epidermis and an objective increase in the collagen fibers in the dermis.

Discussion
This study is the first double-blind vehicle-controlled scientific study conducted on glycolic acid. This study confirms the efficacy of weekly 50% glycolic acid chemical peels in improving rough texture, actinic keratoses, and fine wrinkling seen in photoaged skin. In this study, the beneficial effects of 50% glycolic acid peels on photoaged skin were seen after only four weekly treatments, whereas in one tretinoin study, it took 16 weeks to achieve similar improvement in photoaged skin.

Two different dermatologists were used to evaluate and treat the patients. One dermatologist, who did not know which gel was applied to which side, evaluated the patients at the pretreatment and the posttreatment office visits. A second dermatologist applied the four weekly 50% glycolic acid peels to these patients. Two dermatopathologists evaluated the histologic specimens in a blinded fashion.
On light microscopy, the effects of glycolic acid were evident throughout the epidermal layers. The stratum corneum layer was markedly thinned. The thickening of the granular layer of the epidermis caused by the glycolic acid suggests either an increased proliferation of keratinocytes, or may be due to a nonspecific reaction of the peeling effect. This increase in epidermal thickness may be due to the epidermal stimulation effect of glycolic acid. This finding may suggest that glycolic acid can affect the basal keratinocyte growth of epidermal cells.\textsuperscript{16,17}

The improvement of fine wrinkles may be directly due to the thinning and smoothing of the stratum corneum caused by glycolic acid applications. Similar effects on the stratum corneum have been shown with the use of tretinoin.\textsuperscript{3} Additionally, the thickening of the granular layer and growth of the epidermal layers may be contributing to the improvement in fine wrinkling. In some biopsy specimens, an increase of collagen synthesis was noted, which could contribute to the decrease in fine wrinkling. Coarse wrinkling, however, remained unchanged as was expected after only 4 weeks of treatment. Longer term studies focusing on the dermal effects of glycolic acid need to be conducted to assess its effects on collagen and glycosaminoglycans. From the microscopic examination of the biopsy tissues, the collagen bundles appear thicker and more prominent. Increased desquamation of the old stratum corneum with irregular surfaces is also thought to contribute to decreasing the rough texture of the skin.

Solar lentigines and actinic keratoses were probably improved by the mechanism of discohesion of the UV-altered cells that characterize each lesion. The epidermal stimulation by the glycolic acid peels may contribute to the removal of the lesions by increasing the growth of normal, undamaged cells underneath the lesions. Lightening of the solar lentigines may be attributed to the increased epidermal turnover, since in hyperproliferative epidermis, the individual keratinocytes contain fewer melanosomes. Thinning of the stratum corneum may also contribute to lightening of the skin since each layer of corneocytes, with its melanin, contributes to the color of the skin. Furthermore, excessive pigmentation may be directly decreased by glycolic acid as supported by reports of organic acids directly inhibiting tyrosinase activity in vitro.\textsuperscript{18,19} Glycolic acid only had a very mild effect in skin lightening.

The 50% glycolic acid peels demonstrated equal efficacy in improving rough texture and solar lentigine on all the study areas. This indicates that glycolic acid peels have consistent and equal effects on different anatomic areas.

Of interest was that actinic keratoses were much more effectively treated on the forearms than on the hands or face. It may be recommended to perform 50% glycolic acid chemical peels on the forearm for actinic keratoses. This peel could thin a significant amount of the actinic keratoses to make them more amenable to adjuvant therapy, such as 5-fluorouracil, liquid nitrogen, or trichloroacetic acid.

In summary, glycolic acid has been found to be useful for the treatment of photoaging and for other skin conditions. At this time, this study is the first blinded-controlled scientific study to demonstrate that glycolic acid peels are advantageous in treating sun-damaged skin conditions. This study focuses on the treatment of photodamage that is treated easily and successfully with glycolic acid peels. The peels are easy to apply and are quickly effective. Excellent patient compliance was noted in all 34 patients. This was due to several factors such as: short treatment time, minimal discomfort, and in-office control of application by a physician. Glycolic acid peels have become important in cosmetic procedures and are useful in dermatologic practice. Additionally, the repeated use of glycolic acid peels is a very simple and rapid method of achieving improvements in photodamaged skin with minimal side effects that the patient will readily tolerate. Longer term studies and electron microscopic studies still need to be performed.

**Acknowledgments** Micheal Bastien, MD, and Leo Indianer, MD, provided expert histological assistance. A special thanks to Rosemarie Bessey for her secretarial assistance.

**References**


P.O. Box 810472 • Dallas, Texas 75381 • 972. 620. 9730 • Fax: 972. 421. 1860