The Treatment of Photodamaged Skin With 5% 5-Fluorouracil Peels

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The purpose of this article is to discuss the potential benefit of 5% 5-fluorouracil (5% 5-FU) peels used in conjunction with glycolic acid for the treatment of actinic keratosis (AK) while delivering a cosmetic benefit and to provide a how-to description for clinicians. This article will include a review of published literature, discussion of the author's technique, and presentation of a case series of patients treated in a clinical setting.

Numerous studies have demonstrated that 5% 5-FU effectively reduces the number of AK lesions and improves the appearance of other markers of photodamage. This efficacy is likely due to the peel action enhanced by 5% 5-FU in patients with moderate to large numbers of AKs, which in turn offers improvement in complexion, skin tone, and skin texture. Moreover, patients' skin is often smoother and more homogeneous, giving a clearer field in which to continue skin cancer surveillance. The addition of 5% 5-FU to glycolic acid also offers the added benefit of treating subclinical AK lesions, thereby reducing the likelihood of future AKs. Compliance is also improved over use of 5% 5-FU alone, with a decrease in discomfort time from 4 to 8 weeks of 5% 5-FU use to 1 to 2 weeks downtime postpeel. The combination of 5% 5-FU and glycolic acid also improves patient satisfaction, as patients receive an effective treatment for AKs and see an overall cosmetic improvement.

The 5% 5-FU peel has both therapeutic and cosmetic benefits. Cosmetically and therapeutically, the 5% 5-FU peel avoids the side effects of deeper peels and requires less downtime. Therapeutically, the 5% 5-FU peel may also decrease the likelihood of developing skin cancer in the future. The dual mechanisms of the 5% 5-FU peel may, therefore, increase patient compliance with treatment and medical follow-up.

Actinic keratoses (AKs) are a true medical concern to the dermatologist, not solely a cosmetic issue. The prevention and treatment of photoaging and photodamage may prevent the progression of AKs to squamous cell carcinomas (SCCs). Here is an opportunity for the dermatologist to treat photodamaged skin in a way that not only medically treats an unsightly lesion but also renders a desired cosmetic result at the same time.

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The purpose of this article is to discuss the potential benefit of 5% 5-fluorouracil (5-FU) peels used in conjunction with glycolic acid for the treatment of AKs while leveraging a cosmetic benefit to keep patients compliant with treatment and requiring little downtime. A step-by-step discussion of how to perform the technique will also be presented.

There are numerous modalities available for the treatment of photoaging. The Table displays the most common therapies and their limitations.

5% 5-FU COMPARED WITH CHEMICAL PEELS

Lawrence et al[1] compared the efficacy of 5% 5-FU with Jessner solution and 35% trichloroacetic acid on patients

Treatment Options and Their Limitations

Treatment Options	Cosmetic and Other Issues
Liquid nitrogen (most common therapy)	Risk of dyspigmentation, blister, stinging
5-fluorouracil alone	Pain or irritation, ulcer, burn, downtime, compliance
Imiquimod	Downtime, irritation, cost, flulike symptoms possible if treating large areas
Electrodessication and curettage	Scarring, need local anesthesia
Jessner peel/trichloroacetic acid peel	Downtime, greater degree of peeling
Photodynamic therapy	Burning, stinging, photosensitivity
Laser	Downtime, anesthesia, peeling, pain

with severe bilateral facial actinic damage. The skin of the left side of the face was treated with a single application of Jessner solution and 35% trichloroacetic acid, whereas the skin of the right side of the face was treated with twice-daily applications of 5% 5-FU cream for 3 weeks. Patients were then followed and examined at 1, 6, and 12 months. At the final evaluation, both treatments had reduced the number of visible AKs by 75%.

COMBINING 5% 5-FU WITH CHEMICAL PEELS

Katz[2] described combining 5% 5-FU with chemical peels in a prospective, randomized, controlled, simultaneously symmetrical, paired comparison study of 20 assessable patients. The trial was a split-face evaluation, with patients applying 5% 5-FU plus Jessner solution to one half of the face and Jessner solution alone to the other half of the face weekly for 8 weeks. The author reported that the adverse effects of peel therapy were minimal and that 8 weekly applications of 5% 5-FU plus Jessner solution substantially reduced the number of AKs compared with Jessner solution monotherapy 6 months after treatment. The combined treatment resulted in a mean AK reduction of 88% compared with a mean AK reduction of 15% with Jessner solution alone (Figure 1).

The purpose of a study by Marrero and Katz[3] was to determine if a combination of 5% 5-FU solution and 70% glycolic acid would have greater efficacy than using glycolic acid alone in destroying precancerous AKs and improving the cosmetic appearance of the skin. In this study, 18 patients were treated with 70% glycolic acid on both sides of the face, and the glycolic acid solution was removed after 2 minutes. One half of the face of each patient also received 5% 5-FU in a randomized fashion, and this remained on the skin for 24 hours. The solutions were applied weekly to all patients for an 8-week period. The combination of 5% 5-FU and glycolic acid cleared 92% of AKs after a 6-month follow-up period compared with 20% clearing by glycolic acid alone; there were no significant side effects reported with the combination peel. The authors concluded that the 5% 5-FU peel not only provides cosmetic improvement but, more importantly, has a therapeutic effect on ablating premalignant AKs. This therapeutic effect occurred without the irritation sometimes associated with using 5% 5-FU alone in a typical dosing regimen. It is evident that the superficial peeling induced by α-hydroxy acids (AHAs) not only may improve cosmesis of actinically damaged skin but also can theoretically allow for better penetration of the 5% 5-FU to the hyperkeratotic actinically damaged skin. The authors also found that glycolic acid alone cannot destroy a significant number of AKs.

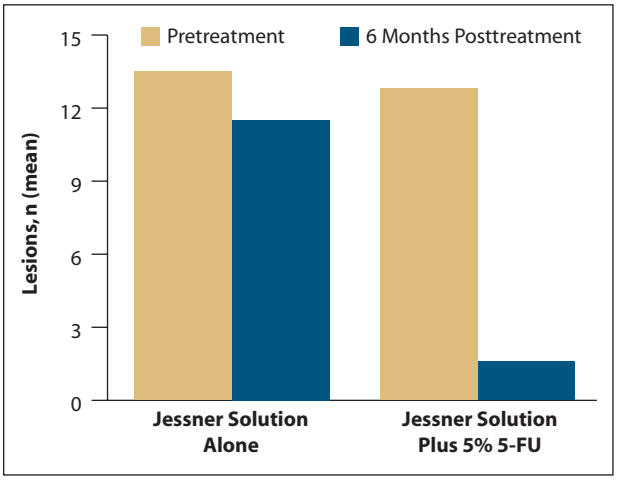

Figure 1. Mean number of actinic keratosis lesions before and 6 months after treatment with Jessner solution alone compared with Jessner solution plus 5% 5-fluorouracil (5-FU).[2]

Jury et al[4] found that daily applications of 5% 5-FU cream were more effective than weekly applications for clearing AKs but that inflammation was likely before achieving a therapeutic effect. Topical FU creams are the most commonly used treatment for AKs; it is well established that 5-FU treatments will result in the lesions becoming increasingly erythematous and causing discomfort. The treatment can be temporarily disfiguring, with ulcerations and crust formation. However, patient compliance is of the utmost importance, as the lesions likely heal within 2 weeks of treatment cessation and the patient's complexion is smooth with an improvement in AKs.[5]

Other topical treatments (such as 5% imiquimod) have side effects similar to those of 5% 5-FU,[6] which may deter patients from completing their initial treatment regimens. Ideally, any AK treatment should reduce downtime and, if side effects are unavoidable, at least minimize the patient's discomfort to help ensure compliance.

DETAILS OF THE AUTHOR'S TECHNIQUE

Patients who are candidates for this technique are those who present for the first time with AKs, those in whom recurrent AKs have been an issue, those who have a history of AKs and are concerned about the pain or cosmesis of other techniques (ie, cryosurgery, electrodessication or curettage, photodynamic therapy), those in whom long courses of topical therapy (ie, 5% 5-FU or imiquimod) are not feasible, or those who have multiple lesions.

It is imperative that these patients understand the importance of follow-up and that the procedure needs to be repeated every 6 months to ensure that the lesions are being treated adequately and are not recurring. Patients also need to be counseled that this chronic surveillance of their skin is helpful in management and is intended for prevention of future disease.

I do not perform this technique on patients who have few AKs, who will not comply with the follow-up as outlined, or who may be suspicious for SCCs. Similarly, if a particular lesion has been treated a number of times and either recurs or is nonresponsive to treatment, then a biopsy is performed to eliminate a diagnosis of skin cancer.

Patients are pretreated with 5% 5-FU cream twice daily for 1 week. Patients are told that they should see some results from the treatment within the first 4 or 5 days. Patients are instructed to avoid applying the cream to the corners of their eyes or the nasal groove, as those areas may become irritated from occlusion. If, after 1 week, there are no visible results from the treatment, patients are reminded to continue treatment with 5% 5-FU for a second week before initiating the peel.

Since patients will not use the full tube of 5% 5-FU cream if they are treating a smaller area such as the face, I request that they keep the tube capped and in a cool medicine cabinet. We remind patients to discard the unused portion after the expiration date.

After 1 week of 5% 5-FU cream, patients return to the office. During this visit, 70% glycolic acid is applied until the epidermis turns white, indicating epidermolysis, which usually occurs within 2 minutes of the 70% free glycolic acid peel application. Immediately after the peel, cold water compresses are applied to the skin and a cold mask is left on for about 5 minutes to address patient comfort issues.

Patient discomfort tolerance is rated on a scale of 0 to 10, with 10 being the highest level of discomfort. The mask is removed when the patient determines the level of discomfort is 0. Patients should be aware that, after the peel, the area involved will look worse before they see any improvement. Patients are told that they will experience some inflammation and irritation of the site, which generally resolves within 1 week after the peel.

The day of the peel, patients are allowed to use acetaminophen to reduce the discomfort that they may experience immediately after the peel. The discomfort generally resolves with icing in the office before patients are discharged, however. The patients are told to apply a moisturizer that will help keep scaling to a minimum. Icing after the procedure is recommended on the first day. Patients should expect scabbing and are reminded not to remove scabs. Typically, patients are referred back to the office 2 weeks after the peel for follow-up.

The author has found this technique to be useful for most patients. Figures 2 through 4 demonstrate what can be expected from application of this technique.

DISCUSSION

The modality of first treating skin with 5% 5-FU for 1 week twice daily and then using a glycolic acid peel shortens downtime, reduces AKs, and improves the overall cosmesis of the skin.[7] In my experience, the combination therapy has been safe and effective and resulted in only minimal discomfort to the patients; discomfort is managed through icing and acetaminophen on the day of the glycolic acid peel.

In general, patients report that using a topical therapy (either 5% 5-FU or imiquimod) solely over the typical course of treatment produces irritating lesions that make the area being treated more obvious, uncomfortable, or both. By adding a glycolic acid peel, patients note that their discomfort is generally limited to the actual peel time. Using 5% 5-FU before treating with the glycolic acid peel provides patients with a faster healing time (≈1 week) than that obtained using 5% 5-FU alone (≈4 weeks).

Figure 2. Patient with actinic keratoses after treatment with 5% 5-fluorouracil cream alone (A) and immediately after (B), 3 days after (C), and 16 days after (D) treatment with 70% glycolic acid peel.

Adequately preparing patients for the peel discomfort and reminding them about over-the-counter pain relief medications such as acetaminophen have led patients in my practice to prefer the combined method to 5% 5-FU or imiquimod alone as a treatment for AKs.

The combination of 5% 5-FU and glycolic acid offers several advantages to patients. The combination reduces the markers of photodamage to a greater extent than does either modality alone. This is probably due to the peel action of glycolic acid enhanced by 5% 5-FU in patients with moderate to large numbers of AKs. Additionally, the combination offers improvement in complexion, skin tone, and skin texture. After the treatment, the skin is smoother and more

Figure 3. Patient with actinic keratoses after treatment with 5% 5-fluorouracil cream alone (A) and 2 weeks after treatment with 70% glycolic acid peel (B).

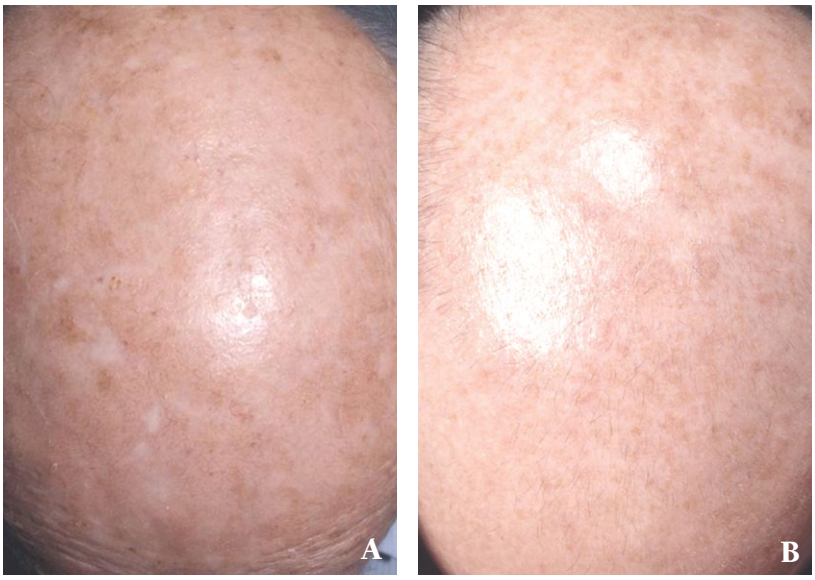

Figure 4. Patient with actinic keratoses after treatment with 5% 5-fluorouracil cream alone (A) and 2 weeks after treatment with 70% glycolic acid peel (B).

homogeneous, creating a clearer field in which to continue skin cancer surveillance.

Patients who can visualize the effects of the treatment before undergoing it are much better prepared for the cosmetic results. Therefore, I like to show patients photographs taken before, during, and after treatment. Moreover, patients like the benefits offered by both treating AKs and simultaneously improving the overall cosmetic appearance of the skin. The improved cosmetic outcome offered by the addition of glycolic acid to 5% 5-FU may also serve to increase patient compliance with 5% 5-FU therapy. When 5% 5-FU is used as monotherapy, patient compliance may be affected by downtime, manifested as inflamed skin over a period of several weeks when the 5% 5-FU is dosed twice daily for up to 4 weeks. Combining 5% 5-FU with a glycolic acid peel reduces patient downtime (inflammation and redness) and increases cosmetic results, which may increase compliance. This increased compliance may aid in the interruption of the continuum of AK to SCC.

The use of 5% 5-FU for the treatment of AKs is well established, and 5% 5-FU has been consistently shown to completely clear more than 90% of AKs with a field effect.[8] The mechanism behind the complementary action of 5% 5-FU with AHAs may be multifactorial[2]: AHAs increase skin permeability, which may enhance penetration of 5% 5-FU, thereby increasing its efficacy. AHAs increase desquamation, which may reduce 5% 5-FU–associated inflammatory reactions. Whereas the 5% 5-FU may target the precancerous lesions, the glycolic acid peel may be the "smart bomb" that aids in the destruction of these premalignant lesions.

CONCLUSION

Improvement of photoaged skin and skin rejuvenation and a shortened period of inflammation and downtime may be beneficial side effects of 5% 5-FU combined with glycolic acid treatment; these effects may improve patient compliance in the treatment of AKs. Application of the 5% 5-FU peel may decrease a patient's likelihood of developing skin cancer in the future.

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