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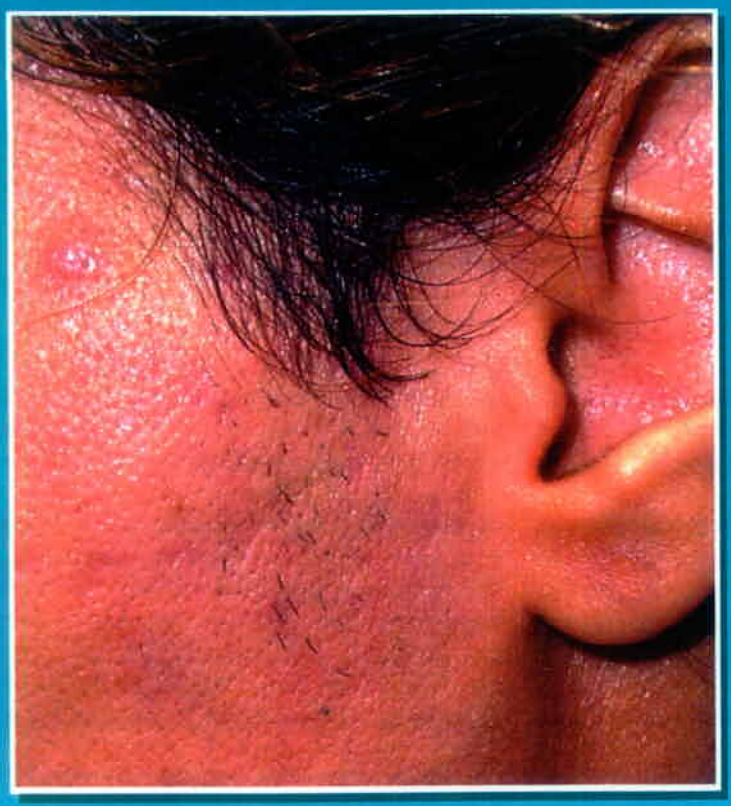

Treatment of Postinflammatory Hyperpigmentation in Skin Types IV–VI

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Study

The Efficacy and Tolerability of a Combination Cream Containing 4% Hydroquinone in the Treatment of Postinflammatory Hyperpigmentation in Skin Types IV–VI

Fran E. Cook-Bolden, MD

This trial assessed the efficacy and safety of a cream (Glyquin®) containing hydroquinone 4%, buffered glycolic acid 10%, vitamin C, vitamin E, and sunscreen in the treatment of 35 patients with postinflammatory hyperpigmentation (PIH) with skin types IV to VI. Participants applied the study cream twice daily for 12 weeks. Pigmentation changes were assessed monthly. Pigmentation severity decreased by week 12 in all patients, and 89% of the patients in the study group reported no significant adverse events. The study cream was effective and well tolerated for 12 weeks in patients with PIH and skin types IV to VI.

Postinflammatory hyperpigmentation (PIH) is defined as an area of skin discoloration (darker than the normal unaffected skin) at the site of a previous inflammatory process. Clinically, PIH can present on almost any area of the body and is commonly seen on the face, trunk, or extremities as brown-to-black macules and patches that assume the shape, size, and distribution of the preceding dermatosis.[1] The intensity of the hyperpigmentation may be related to both the nature of the preceding dermatosis and the degree of prior inflammation.

Either endogenous or exogenous inflammatory processes may cause PIH. Endogenous causes can arise from (1) dermatological diseases, such as acne, atopic dermatitis, lichen planus, and erythema dyschromicum perstans or (2) systemic diseases that induce cutaneous pigmentation, such as morphea, discoid lupus erythematosus, or porphyria. Exogenous causes include exposure to (1) sunlight or ionizing radiation; (2) chemicals, such as essential oils (eg, bergamot) used in perfumes[2]; (3) fixed drug eruptions secondary to medicines, such as laxatives containing phenolphthalein,[3] antimalarial drugs,[2] and certain tetracyclines[2]; or (4) inflammation from acne treatments, such as benzoyl peroxide or retinoids.[4] PIH is a common consequence of mechanical trauma to the skin, such as aggressive laser resurfacing procedures.[5] In a study of 22 patients with Fitzpatrick skin type IV who had undergone CO_2 or Er:YAG laser resurfacing, PIH was reported in 68% of the patients.[6] Another precursor to inflammation is contact dermatitis due to exposure to irritants, such as sodium lauryl sulfate,[2] and allergens, such as nickel in jewelry[2] and paraphenylenediamine, found in color film developer[2] or in henna used for temporary tattoos.[7]

The disorder can be a major concern for patients with Fitzpatrick skin types IV to VI, in whom PIH is most prevalent. In a study that included 2000 African American patients, PIH was the third most common presenting diagnosis.[8] Treatment of PIH involves the use of broad-spectrum sunscreens, pharmacological agents, and/or superficial peeling agents. Hydroquinone (HQ), the agent most widely used to treat PIH, functions to inhibit up to 90% of the activity of the enzyme tyrosinase,[9] slowing the conversion of L-dopa to melanin.

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A cream (Glyquin®) containing HQ 4%, buffered glycolic acid 10%, vitamin C, vitamin E, and sunscreen previously has been shown to be successful in treating epidermal melasma of the face.[10] According to Berardesca et al,[11] glycolic acid may reduce the thickness of the stratum corneum. Ascorbyl palmitate (vitamin C) and tocopherol acetate (vitamin E) reduce erythema induced by UV exposure.[12] Vitamin C also may provide an additional lightening effect on skin pigmentation by maintaining melanin in its reduced (nonoxidized) state.[13] In addition, the study preparation is notable in that it does not expose the patient to sodium metabisulfite, a preservative that is a known allergen,[14] particularly in patients with asthma.[15] The objective of this study was to assess the efficacy and safety of this combination of ingredients in treating PIH on the face and body of patients with Fitzpatrick skin types IV to VI.

Methods

This study was conducted in compliance with the Declaration of Helsinki, 1996. Study participants gave informed consent prior to initiation of any study-related procedures. The study was performed in compliance with informed consent regulations (US 21 CFR, part 50).

Eligibility Criteria

Patients with a clinical diagnosis of PIH of the face or body with Fitzpatrick skin types IV to VI were recruited for the study. Exclusion criteria included: (1) exposure within 2 weeks prior to baseline to a topical corticosteroid, bleaching product, azelaic acid, α-hydroxy acid or β-hydroxy acid, retinoid, UV light therapy, or sunbathing; (2) treatment with oral systemic corticosteroids within 30 days, systemic retinoids within 120 days, or other systemic photosensitizing drugs within 120 days; (3) patients who would require concomitant topical therapy that would interfere with the study; (4) patients with a suntan or those who would expose the target area to the sun on a regular basis; (5) known sensitivity to the study cream or any of its ingredients; (6) participation in an investigational study in the previous 30 days; (7) patients with melasma; or (8) patients who were immunocompromised.

Study Design

After a 4-week washout period, the patients underwent a baseline evaluation, including an initial examination, to confirm the diagnosis of PIH. They were then assessed at weeks 4, 8, and 12. Patients applied the study cream containing HQ 4%, buffered glycolic acid 10%, vitamin C, vitamin E, and sunscreen twice daily to the involved areas for the 12-week study period and recorded missed doses in a special calendar. Photographs were taken at baseline and at each monthly visit under standard conditions. Reflectance spectrophotometer readings of pigmentation and erythema were performed on both the target lesion and normal untreated skin at each evaluation using the Mexameter®. At each visit, the average of 3 mexameter readings was recorded from the target lesion and normal untreated skin sites.

Patients and physicians assessed pigmentation severity at each visit, using a 4-point visual scale (1=none, 2=mild, 3=moderate, 4=severe). The investigator graded irritation at each visit, using both objective (erythema, scaling/peeling, edema, crusting, erosions) and subjective (burning, itching, pain, overall irritation) measures on a 5-point scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe). Both patients and physicians assessed improvement from baseline, using a 5-point scale at each follow-up visit (*resolved, significant improvement, slight improvement, no change,* or *worsening*). The assessment was made with photographs taken at baseline. Adverse events were assessed at all visits.

Patients were instructed that skin care during the study would consist only of a specific moisturizer as needed, a specific cleanser twice daily, and a particular SPF 25 sunblock daily, together with strict instructions to avoid the sun.

Baseline and posttreatment pigmentation differences were analyzed using 2-sided, paired *t* tests with α=.05.

Demographics and Baseline Characteristics

Number of Participants	35
Age range, y	23–62
Sex	
Male	1
Female	34
Skin types	IV–VI
Postinflammatory Hyperpigmentation Etiology, n (%)	
Acne	21 (60)
Irritation	6 (17)
Trauma	2 (6)
Other dermatoses	6 (17)
Minimally Responsive or Nonresponsive to Prior Hydroquinone Therapy, n (%)	24 (69)

Results

Study Population

A total of 35 patients (34 female, 1 male) with PIH and Fitzpatrick skin types IV to VI enrolled in the study, with

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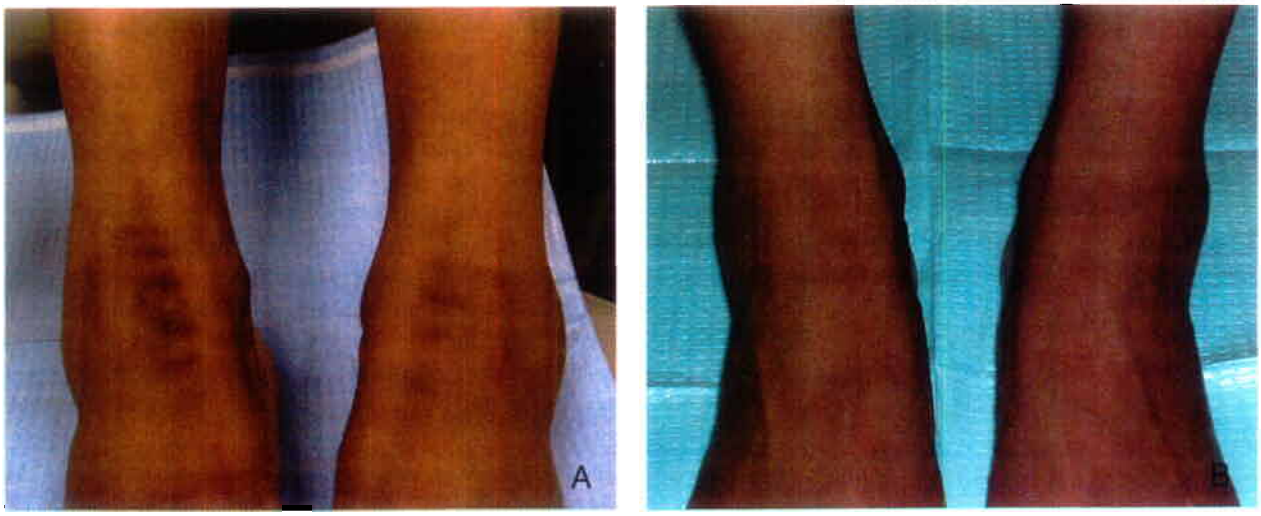

Figure 1. Pigmentation severity of ankles: (A) at baseline and (B) after 12 weeks of treatment. Reprinted with permission from *Cosmet Dermatol.* July 2003;16:33-35. © 2003, Quadrant HealthCom Inc.

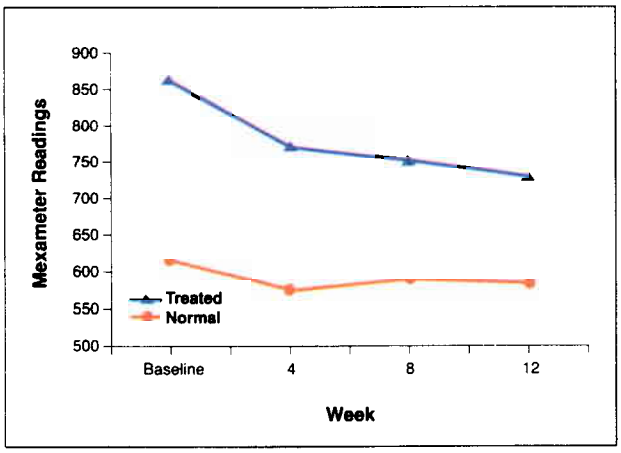

Figure 2. Mexameter averages: after 12 weeks of treatment with the study cream, 100% of patients demonstrated improvement in pigmentation in the target areas ($P<.001$) but not in the untreated areas ($P=.178$). The mean Mexameter reading decreased by 165.3 points in the treated area versus 25.8 points in the untreated area.

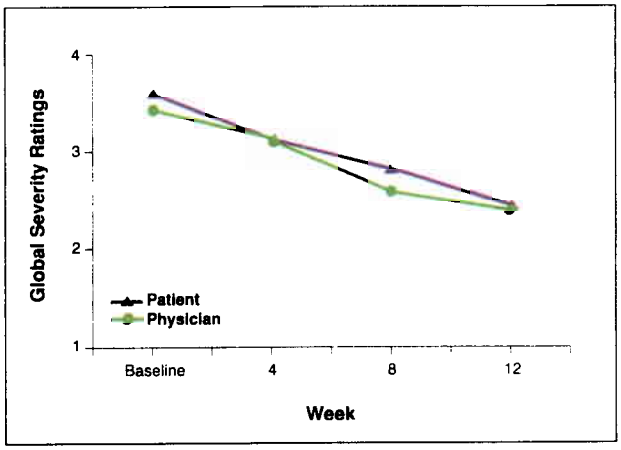

Figure 3. The patient assessment of pigmentation severity (on a 4-point visual scale) improved significantly, from a mean of 3.6 points at baseline to a mean of 2.4 points after 12 weeks ($P<.001$). The patient assessment of pigmentation severity improved by 2 points in 8/25 patients (32%) and by 1 point in 11/25 patients (44%). Similarly, the physician assessment of pigmentation severity fell from a mean of 3.4 points at baseline to a mean of 2.4 points ($P<.001$). Physician assessment of pigmentation severity improved by 2 points in 6/25 patients (24%) and by 1 point in 14/25 patients (56%).

ages ranging from 23 to 62 years. The etiology of the PIH was as follows: acne (60%, 21/35), irritation (17%, 6/35), trauma (6%, 2/35), and other dermatoses (17%, 6/35). The areas treated in the 35 patients were: face/neck (20), trunk (5), upper extremities (6), and lower extremities (5). One patient had lesions on both the face and trunk. In the study group, 69% (24/35) had been minimally responsive or not responsive to previous HQ therapy (Table). Of the total study group of 35, 10 were lost at follow-up or because treatment was discontinued because of unrelated problems or minor skin irritation.

A comparison of pigmentation on the ankles of a patient at baseline and after 12 weeks of treatment is shown in Figure 1. Based on Mexameter readings, improvement in pigmentation levels was seen in treated target areas within as little as 4 weeks. After 12 weeks of treatment with the study cream, Mexameter results (Figure 2) demonstrated a significant decrease from baseline in the degree of pigmentation at the sites treated with the study cream ($P<.001$) but not at the untreated areas ($P=.178$). The mean Mexameter reading decreased by 165.3 points in the treated area versus only 25.8 points in the untreated area.

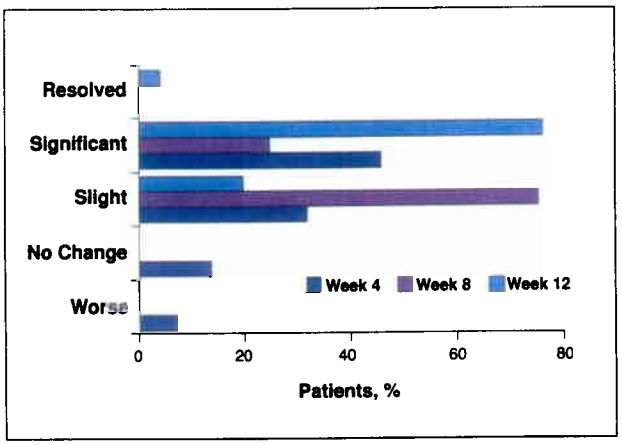

Figure 4. The physician assessment showed 80% (20/25) of patients, after 12 weeks of treatment, demonstrated significant improvement or resolution of their PIH lesions, relative to baseline.

The patient assessment of pigmentation severity (Figure 3), a 4-point visual scale, improved significantly after week 12 from a mean of 3.6 at baseline to a mean of 2.4, an average improvement of 1.2 points ($P<.001$). Similarly, the physician assessment of pigmentation severity fell, from a mean of 3.4 at baseline to a mean of 2.4 after week 12 ($P<.001$).

According to the physician assessment, by week 4, 47% (15/32) of the patients had achieved a substantial improvement, and another 31% (10/32) had achieved a slight improvement. By week 8, 100% (25/25) of the patients had achieved either a slight or a substantial improvement. By week 12, 76% (19/25) of the patients had achieved a substantial improvement, while 20% (5/25) had achieved a slight improvement; for the remaining 4% (1/25), hyperpigmentation was resolved completely (Figure 4).

Overall, patients tended to perceive their improvement as better than the physician assessments. After 12 weeks, physicians assessed 24% (6/25) of patients with a 2-point improvement in pigmentation severity and 56% (14/25) of patients with a 1-point improvement. In contrast, 32% (8/25) of patients assessed themselves with a 2-point improvement in severity, and 44% (11/25) perceived a 1-point improvement.

Adverse Events

Adverse events were infrequent during the course of the study, with 89% (31/35) of the patients reporting either minimal to mild or no symptoms. The most common adverse events were minimal burning, irritation, or itching with a frequency that peaked at week 4 and then declined. By week 12, only 8% (2/25) of patients experienced burning, 8% (2/25) reported irritation, and none reported itching.

Comment

In this study, patients with Fitzpatrick skin types IV to VI treated with a cream containing HQ 4%, buffered glycolic acid 10%, vitamin C, vitamin E, and sunscreen experienced a statistically significant improvement in PIH after 12 weeks. This was demonstrated with both objective Mexameter readings and patient and physician assessments of clinical improvement. A majority of patients, (84%, 21/25), tolerated this formulation very well and experienced minimal or no adverse events during treatment.

PIH is a major concern, especially among patients with Fitzpatrick skin types IV to VI. Although other modalities have been used to treat PIH in patients with dark skin (eg, tretinoin[16] and chemical peels[17]), HQ is the most commonly used agent for treatment of PIH. HQ interferes with the conversion of L-dopa to melanin via inhibition of the enzyme tyrosinase.

To the author's knowledge, HQ 4% in combination with glycolic acid 10% has not been tested for PIH in skin types IV to VI, though a glycolic acid 10% peel with HQ 2% was effective in treating 19 African American patients with PIH.[18] The current study cream (combination of HQ 4%, buffered glycolic acid 10%, vitamin C, vitamin E, and sunscreen) was proven successful in treating epidermal melasma of the face in 39 Hispanic women treated for 12 weeks.[10] HQ 4%, in concert with glycolic acid peels (20% to 30% concentration) every 2 weeks for 8 weeks, was effective in treating melasma in 21 Hispanic women.[19] A glycolic acid 10% peel containing HQ 2% was effective in treating melasma in 10 Chinese women treated for 26 weeks.[20]

In the study cream formulation, glycolic acid may reduce the thickness of the stratum corneum barrier.[21] In addition, vitamin C may provide an additional lightening effect on skin pigmentation by maintaining melanin in its reduced (nonoxidized) state.[13] Vitamin C also protects cell membranes from peroxidation by enhancing the antioxidant activity of vitamin E.[22]

In the future, compounds containing even stronger moisturizers, such as hyaluronic acid, and sunscreens may prove to be even less irritating while providing equal efficacy in the treatment of disorders of hyperpigmentation.

Conclusion

The study cream containing HQ 4%, buffered glycolic acid 10%, vitamin C, vitamin E, and sunscreen is effective in decreasing PIH in target areas on the face and body in patients with Fitzpatrick skin types IV to VI. Findings indicate the study cream is safe and well tolerated.

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References

1. Freedberg IM, Eisen AZ, Wolff K, et al, eds. *Fitzpatrick's Dermatology in General Medicine*. 6th ed. Maidenhead. United Kingdom: McGraw-Hill Professional; 2003.
2. Epstein JH. Postinflammatory hyperpigmentation. *Clin Dermatol*.1989;7:55-65.
3. Kenney JA Jr. Pigmentary disorders in black skin. *Clin Dermatol*.1989;7:1-10.
4. Grimes PE, Stockton T. Pigmentary disorders in blacks. *Dermatol Clin*. 1988;6:271-281.
5. Lent WM, David LM. Laser resurfacing: a safe and predictable method of skin resurfacing. *J Cutan Laser Ther*. 1999;1:87-94.
6. Sriprachya-anunt S, Marchell NL, Fitzpatrick RE, et al. Facial resurfacing in patients with Fitzpatrick skin type IV. *Lasers Surg Med*. 2002;30:86-92.
7. Chung WH, Wang CM, Hong HS. Allergic contact dermatitis to temporary tattoos with positive para-phenylenediamine reactions: report of four cases. *Int J Dermatol*. 2001;40:754-756.
8. Halder RM, Grimes PE, McLaurin CI, et al. Incidence of common dermatoses in a predominantly black dermatologic practice. *Cutis*. 1983;32:388-390.
9. Nordlund JJ. Postinflammatory hyperpigmentation. *Dermatol Clin*. 1988;6:185-192.
10. Guevara IL, Pandya AG. An assessment of the safety and efficacy of a cream containing 4% hydroquinone, 10% buffered glycolic acid, vitamins C and E, and sunscreen versus a cream containing sunscreen only in depigmenting epidermal melasma of the face. Poster presented at: Annual Meeting of the American Academy of Dermatology; February 24-27, 2002; New Orleans. La.
11. Berardesca E, Distante F, Vignoli GP, et al. Alpha hydroxyacids modulate stratum corneum barrier function. *Br J Dermatol*. 1997;137:934-938.
12. Dreher F, Gabard B, Schwindt DA, et al. Topical melatonin in combination with vitamins E and C protects skin from ultraviolet-induced erythema: a human study in vivo. *Br J Dermatol*. 1998;139:332-339.
13. Denton C, Lerner AB, Fitzpatrick TB. Inhibition of melanin formation by chemical agents. *J Invest Dermatol*. 1952;18:119-135.
14. Tucker SC, Yell JA, Beck MH. Allergic contact dermatitis from sodium metabisulfite in Trimovate cream. *Contact Dermatitis*. 1999;40:164.
15. Evans DJ, Coulby LJ, O'Connor BJ. Effect of allergen challenge on airway responsiveness to histamine and sodium metabisulphite in mild asthma. *Thorax*. 1996;51:1185-1191.
16. Bulengo-Ransby SM, Griffiths CE, Kimbrough-Green CK, et al. Topical tretinoin (retinoic acid) therapy for hyperpigmented lesions caused by inflammation of the skin in black patients. *N Engl J Med*. 1993;328:1438-1443.
17. Grimes PE. The safety and efficacy of salicylic acid chemical peels in darker racial-ethnic groups. *Dermatol Surg*. 1999;25:18-22.
18. Burns RL, Prevost-Blank PL, Lawry MA, et al. Glycolic acid peels for postinflammatory hyperpigmentation in black patients: a comparative study. *Dermatol Surg*. 1997;23:171-174. Discussion 75.
19. Hurley ME, Guevara IL, Gonzales RM, et al. Efficacy of glycolic acid peels in the treatment of melasma. *Arch Dermatol*. 2002;138:1578-1582.
20. Lim JT, Tham SN. Glycolic acid peels in the treatment of melasma among Asian women. *Dermatol Surg*. 1997;23:177-179.
21. Effendy I, Kwangsukstith C, Lee JY, et al. Functional changes in human stratum corneum induced by topical glycolic acid: comparison with all-trans retinoic acid. *Acta Derm Venereol*. 1995;75:455-458.
22. Sies H, Stahl W, Sundquist AR. Antioxidant functions of vitamins: vitamins E and C, beta-carotene, and other carotenoids. *Ann N Y Acad Sci*. 1992;669:7-20.