A Microsponge Formulation of Hydroquinone 4% and Retinol 0.15% in the Treatment of Melasma and Postinflammatory Hyperpigmentation

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Disorders of hyperpigmentation such as melasma and postinflammatory hyperpigmentation (PIH) are common, particularly among people with darker skin types. Hydroquinone (HQ) bleaching creams are considered the gold standard for treating hyperpigmentation. Recently, a new formulation of HQ 4% with retinol 0.15% entrapped in microsponge reservoirs was developed for the treatment of melasma and PIH. Microsponges were used to release HQ gradually to prolong exposure to treatment and to minimize skin irritation. The safety and efficacy of this product were evaluated in a 12-week open-label study. A total of 28 patients were enrolled, and 25 completed the study. Study end points included disease severity, pigmentation intensity, lesion area, and colorimetry assessments. Adverse events also were recorded. Patients applied the microentrapped HQ 4% formulation to the full face twice daily (morning and evening). A broad-spectrum sunscreen was applied once in the morning, 15 minutes after application of the test product. Patients were evaluated at baseline and at 4, 8, and 12 weeks. The microentrapped HQ 4%/retinol 0.15% formulation produced improvement at all study end points. Improvement in disease severity and pigmentation intensity was statistically significant at weeks 4, 8, and 12 compared with baseline (P<.001). Lesion area and colorimetry measurements also were significantly improved at each visit (P<.001). Microentrapped HQ 4% was well tolerated, with only one patient discontinuing because of an allergic reaction, which was not considered serious. In this open-label study, microentrapped HQ 4% with retinol 0.15% was safe and effective.

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Pigmentation disorders such as melasma and postinflammatory hyperpigmentation (PIH) are often difficult to treat and can be distressing for patients. Melasma is characterized by symmetric brown or gray-brown patches that appear on sun-exposed areas, particularly on the forehead, cheeks, upper lip, and chin. The precise cause of melasma is unknown. However, intense UV light exposure, hormones (endogenous and exogenous), familial predisposition, photosensitizing medications, and endocrine dysfunction have been implicated in the pathogenesis of this condition. Exposure to UV radiation from the sun substantially increases the risk for developing melasma and exacerbates existing melasma.[1,2] PIH is characterized by dark patches of pigmentation that develop

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Patient Demographics (N=28)

	No. of Patients (%)
Race	
Black	18 (64.3)
White	5 (17.9)
Hispanic	5 (17.9)
Skin classification	
II	4 (14.3)
III	4 (14.3)
IV	8 (28.6)
V	9 (32.1)
VI	3 (10.7)

owing to trauma, inflammation of the skin, or both. Common causes include inflammatory diseases such as acne, eczema, allergic contact dermatitis, psoriasis, and drug eruptions. PIH occurs at the site of skin injury, which can appear anywhere on the body.

The incidence of disorders of hyperpigmentation is unknown, but they are common, particularly among people with darker skin types.[2-6] A study of black patients found that pigment disorders were cited as the third most common reason for seeking dermatologic treatment.[3] Darker racial or ethnic populations residing in areas of intense UV exposure have the highest prevalence of melasma.[2,5] The incidence of melasma among Asian people has been reported to be as high as 40% in women and 20% in men and may account for up to 4% of visits to the dermatologist.[7] Most patients with melasma are women, but men may account for roughly 10% of cases.[1,8,9] There does not appear to be a gender difference in the incidence of PIH.

Hydroquinone (HQ) bleaching creams are considered the gold standard for treating hyperpigmentation. These agents contain a hydroxyphenolic component that inhibits tyrosinase, thereby preventing melanogenesis.[10,11] Melasma is treated most commonly with HQ formulations, ranging in concentrations from 2% available in over-the-counter remedies to 4% available by prescription.[4] Retinol, a pure active form of vitamin A, has become an increasingly common agent in the treatment of aging skin and hyperpigmentation.[12] Retinol promotes normalization and rapid exfoliation of keratinocytes. Current data suggest that retinol is converted to retinoic acid in the skin.[13]

Recently, a new formulation of HQ 4% plus retinol was developed for the treatment of melasma and PIH (SkinMedica). The formulation tested consisted of HQ USP 4% and retinol incorporated into patented porous microspheres (Microsponge® system) composed of methyl methacrylate/glycol dimethacrylate cross-linked polymers. This polymeric system provides gradual release of active ingredient into the skin, prolonging exposure to treatment and minimizing skin irritation.[14] Approximately 2.5% of the HQ is microentrapped and 1.5% is in free-form. Retinol is added in the microentrapped form, and the total concentration is 0.15%. An open-label study was conducted to evaluate the efficacy and safety of this new HQ 4% formulation.[15]

METHODS

Study Design

This was a 12-week open-label study designed to evaluate the safety and efficacy of a new formulation of HQ 4% and retinol 0.15% delivered using microsponge spheres.[15] The study was approved by the institutional review board. Written informed consent and photographic release were obtained for each patient before participation in this study. The study design included a baseline visit and follow-ups at weeks 4, 8, and 12. At the baseline visit, clinicians examined patients to determine the presence and severity of melasma or PIH. Wood light examination was used to assess the depth of pigmentation.

Treatment Protocol

Study participants washed their face with Cetaphil® cleanser before application of study medication. The microentrapped HQ 4%/retinol 0.15% formulation was applied to the entire face twice daily, once in the morning and once in the evening. A broad-spectrum sunscreen (Ombrelle® SPF 30) was then applied to the entire face, 15 minutes after the morning application of microentrapped HQ 4%.

Inclusion and Exclusion Criteria—Inclusion criteria included patients 18 years or older with Fitzpatrick skin types I through VI.[1] Patients had to be clinically diagnosed by the investigator to have mild to moderate melasma or PIH. Patients were excluded if they had dermal melasma or dermal PIH, vitiligo, uncontrolled systemic disease, any condition necessitating UV light therapy, or a concomitant disease that might interfere with the diagnosis of facial hyperpigmentation. Patients also were excluded if they did not meet any one of the inclusion criteria. Women could not be lactating or pregnant, as verified by a negative pregnancy test, and had to state that they were using nonhormonal methods to avoid

conception. Other exclusion criteria included use of any form of bleaching cream, glycolic acid, kojic acid, azelaic acid, tretinoin, retinol, topical steroids, oral contraceptives, or hormonal therapies less than 4 weeks before study initiation. Patients who used HQ for 3 months or more at any time with no clinical response or had sensitivity to HQ were excluded. Patients were not included in the study if they were unable or unwilling to wear sunscreen daily during the study.

Efficacy and Safety Measurements

Study end points included disease severity, pigmentation intensity, lesion area, and colorimetry measurements, which also were recorded at each visit, along with adverse events. Lesion area and pigmentation intensity were rated separately using the following scale: none (0), trace (1), mild (2), moderate (3), marked (4), and severe (5).

Disease severity was graded as none (0, 1), mild (2, 3), moderate (4, 5), marked (6, 7), or severe (8). Global evaluation was performed at 4, 8, and 12 weeks to compare the overall appearance of treated areas to lesions at baseline. Global responses were graded as 0 (worse), 1 (slightly worse), 2 (unchanged), 3 (slight improvement), 4 (mild improvement), 5 (moderate improvement), 6 (marked improvement), 7 (almost complete clearing of disease), or 8 (complete clearing of disease).

A reflectance spectrophotometer (Mexameter® MX 16) measured the pigmentation of a targeted facial lesion at each visit. Measurements were taken in triplicate to obtain an average at each visit.

Adverse Events

Signs of skin irritation, such as dryness, erythema, peeling, burning, and pruritus, were recorded at each visit after initiation of study medication. A 6-point scale was used to assess signs and symptoms of irritation: 0 (none), 1 (trace), 2 (mild), 3 (moderate), 4 (marked), and 5 (severe).

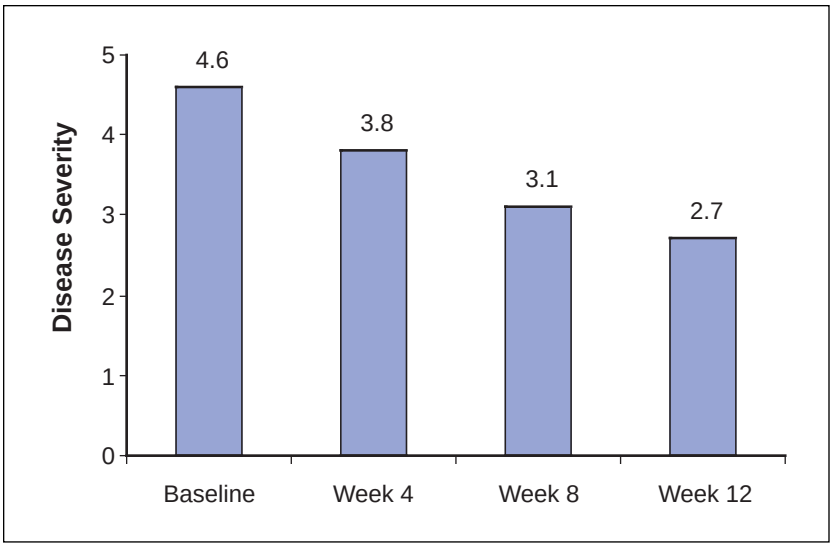


Figure 1. The mean disease severity rating at baseline was moderate. There was improvement in disease severity scores at 4, 8, and 12 weeks. The change from baseline was statistically significant at each time point ($P<.001$). Disease severity was rated on a scale from 0 (none) to 8 (severe).

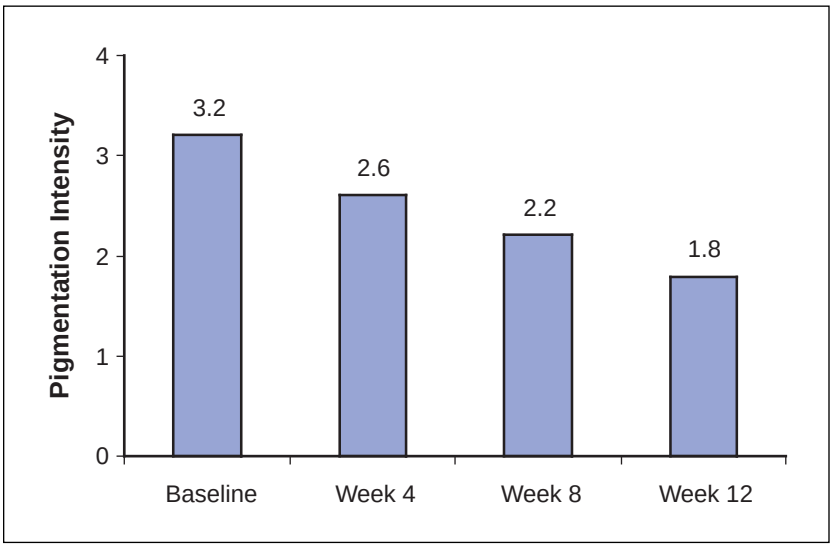


Figure 2. There was statistically significant improvement in pigmentation intensity at 4, 8, and 12 weeks vs baseline ($P<.001$). Pigmentation intensity was rated on a scale from 0 (none) to 5 (severe).

Statistical Analysis

Statistical tests were 2 sided and interpreted at a 5% significance level. Comparisons between baseline and each follow-up visit (within group differences) were performed using a paired *t* test.

RESULTS

The study initially enrolled 19 patients, with 9 more added during an extension phase. Of this

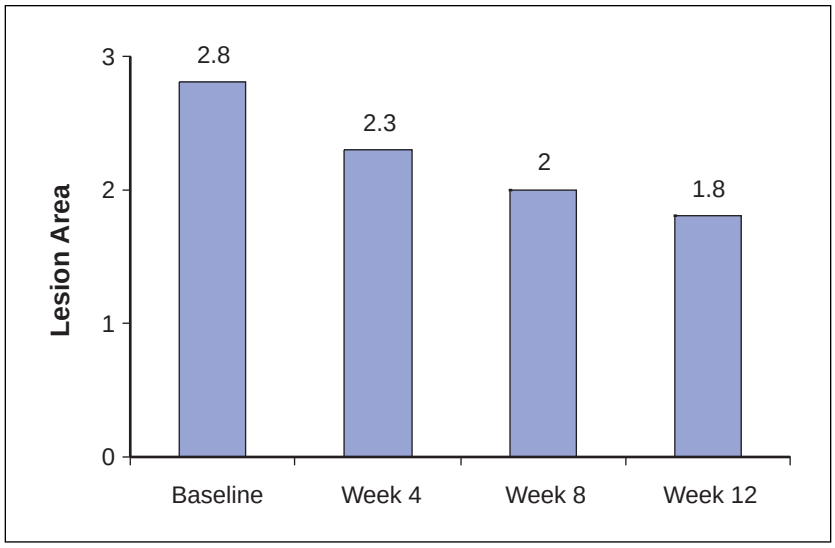


Figure 3. The mean lesion area at baseline represented moderate facial involvement. There was improvement in lesion area at each time point. Change from baseline in lesion area was statistically significant at 4, 8, and 12 weeks ($P<.001$). Lesion area was rated on a scale from 0 (none) to 5 (severe, >50% of the face).

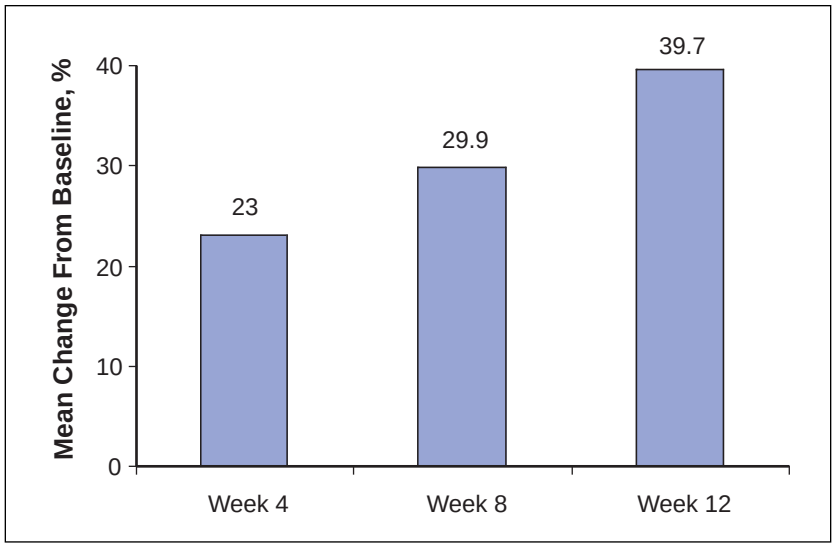


Figure 4. Colorimetry measurements at 4, 8, and 12 weeks. The change from baseline was significant at each time point ($P<.001$).

total of 28 patients, 16 had melasma and 12 had PIH. Twenty-five were women and 3 were men. The mean age was 41 years. Racial designation and skin type are summarized in the Table. Twenty-five patients completed the study.

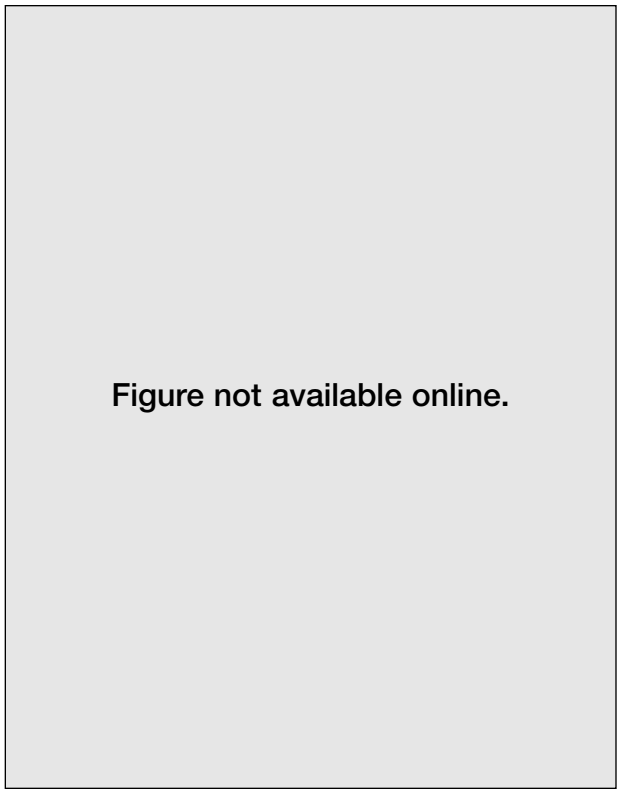
Microentrapped HQ 4% produced improvement at all study end points. There was statistically significant improvement in disease severity (Figure 1) and pigmentation intensity (Figure 2) at weeks 4, 8, and 12 compared with baseline ($P<.001$). Lesion area (Figure 3) and colorimetry measurements (Figure 4) also improved significantly at each visit ($P<.001$). Physician global assessment showed continued improvement in facial hyperpigmentation at each visit compared with baseline. At weeks 4, 8, and 12, moderate to marked improvement was achieved in 39%, 77%, and 77% of patients, respectively. Photographs illustrating baseline disease severity and treatment results are shown in Figures 5 through 7.

Microentrapped HQ 4% also was well tolerated. Signs and symptoms of irritation, including dryness, erythema, peeling, burning, and pruritus, were minimal and not statistically significant throughout the study. Only one patient discontinued because of an allergic reaction to the formulation, which was not considered serious. One patient had a severe reaction to the product characterized by diffuse erythema and scaling. No patch testing was done to determine whether this was a true allergic reaction and not an irritant reaction. Two patients were discontinued because of noncompliance.

Comment

Melasma and PIH are therapeutically challenging diseases. Medical therapies include HQ, kojic acid, azelaic acid, tretinoin, glycolic acid, arbutin, ascorbic acid, mequinol, and licorice.[16] Recently, new combination agents have been approved by the US Food and Drug Administration and marketed for the treatment of hyperpigmentation. Some of these combination agents include HQ 4%, tretinoin 0.05%, and fluocinolone 0.01%; HQ 4% and retinol 0.3%; HQ 4% and Tyrostat™; HQ 4% and glycolic acid 10%; and HQ 4%, glycolic acid 10%, and hyaluronic acid.

In a recent study,[17] the safety and efficacy of a triple combination of tretinoin 0.05%, HQ 4%, and fluocinolone 0.01% were compared with dual combination agents of tretinoin plus HQ, tretinoin



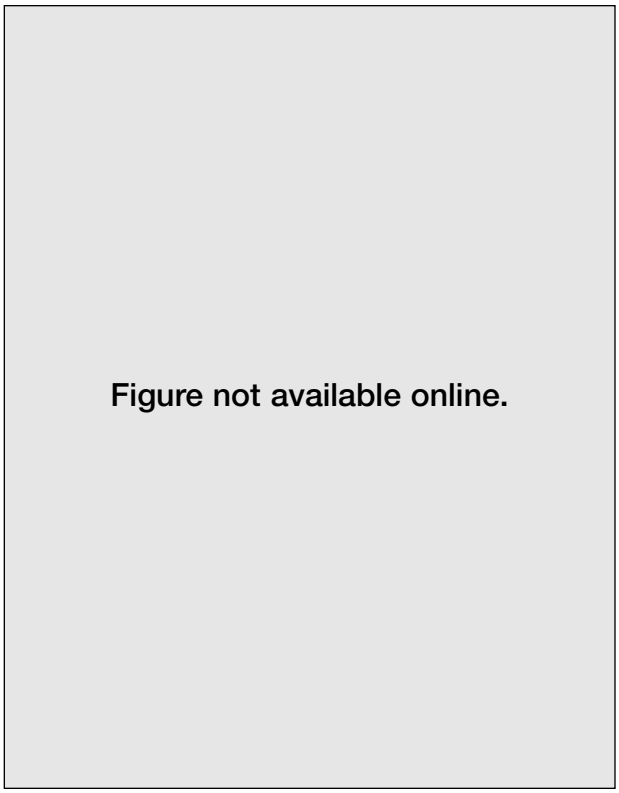
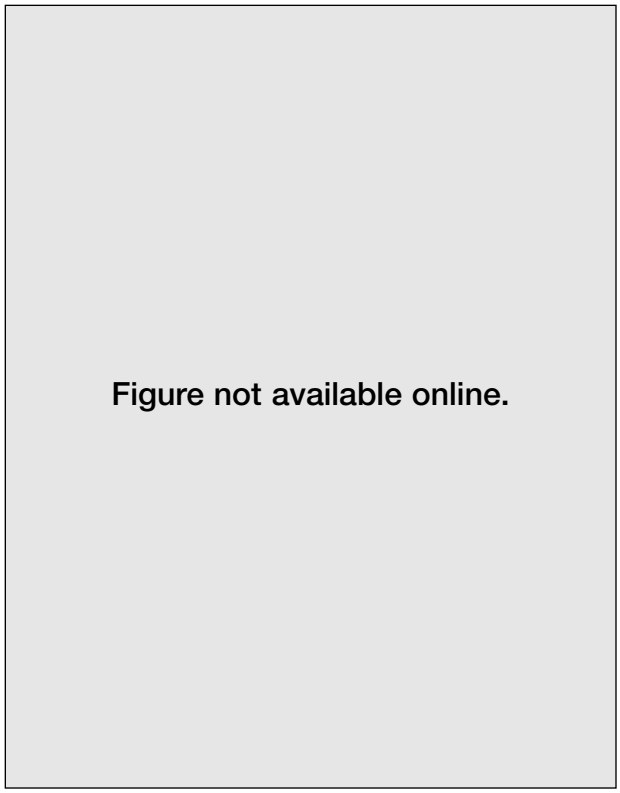


Figure 5. Patient with melasma at baseline (A) and after 4 weeks (B) of treatment with microentrapped HQ 4%. The patient had a global score of 6 (marked improvement) at 4 weeks.



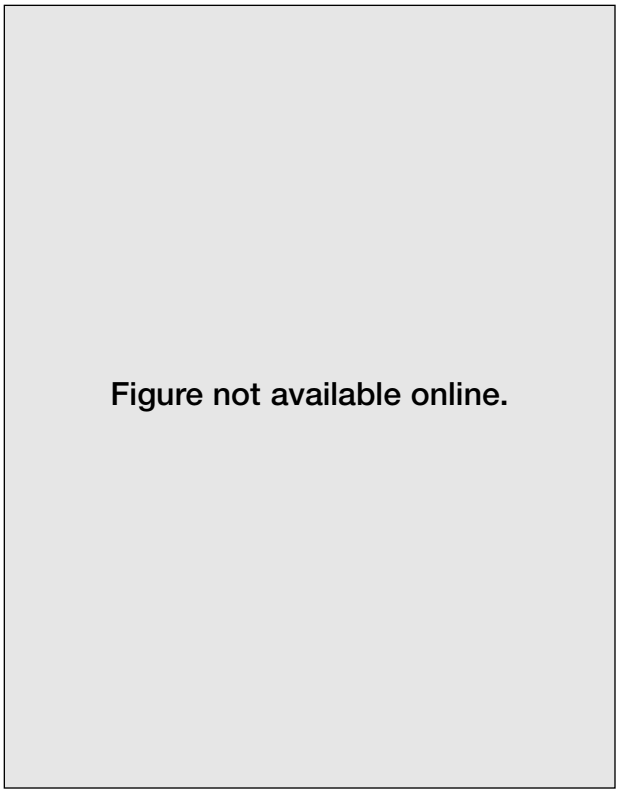


Figure 6. Patient with postinflammatory hyperpigmentation at baseline (A) and after 8 weeks (B) of treatment with microentrapped HQ 4%. The patient had a score of 7 (almost complete clearing of disease) at 8 weeks.

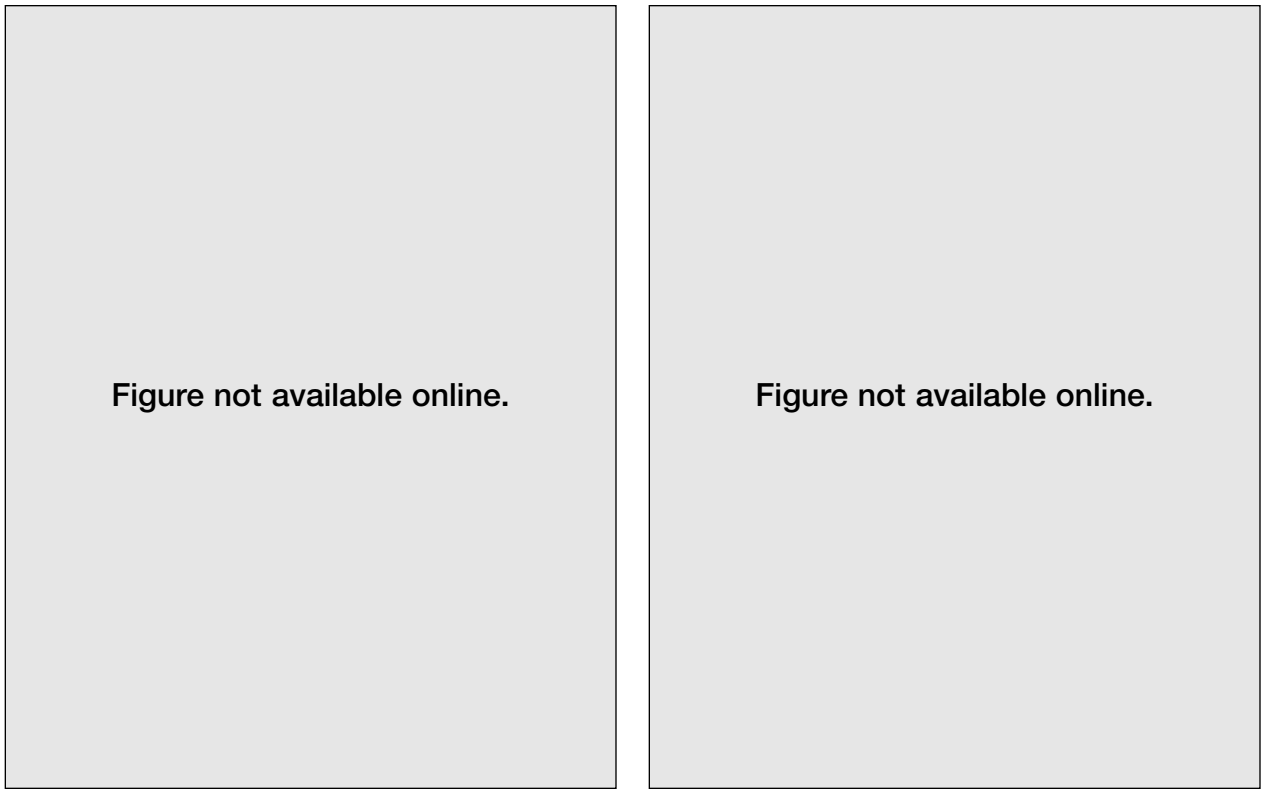


Figure 7. Patient with melasma at baseline (A) and after 12 weeks (B) of treatment with microentrapped HQ 4%. The patient had a global score of 6 (marked improvement) at 12 weeks.

plus fluocinolone, and HQ plus fluocinolone. At week 8, 70% of patients had experienced a 75% reduction in melasma when using the triple combination product versus 30% in patients treated with dual combination agents. Results from this open-label study of microentrapped HQ 4% with retinol showed efficacy in disease severity, pigmentation intensity, lesion area, and colorimetry measurements. Notably, efficacy was achieved as early as 4 weeks; this is significant because treatment of melasma and PIH commonly takes several months. Patients included in the study generally had a moderate level of hyperpigmentation. The improvement at all study end points compared with baseline suggests that this microentrapped HQ 4% is an appropriate choice for first-line therapy of mild to moderate PIH and melasma.[17]

The study also showed that microentrapped HQ 4% with retinol is safe and well tolerated. During the course of the 12-week study, only one allergic reaction and no serious adverse events were noted. The long-term efficacy and safety of microentrapped HQ 4% also may provide a maintenance treatment option in patients using other combination corticosteroid-based formulations in moderate to severe disease.[17] Because daily use of some of these formulations must be discontinued after 8 to 12 weeks to avoid steroid-related side effects, HQ 4% with retinol may provide additional long-term and maintenance therapy for melasma and PIH.

It is likely that the use of microsponges for delivery of HQ and retinol reduces potential undesirable side effects such as erythema and desquamation.

CONCLUSION

Results of this open-label investigation suggest that this new microentrapped HQ 4% and retinol 0.15% formulation provides enhanced efficacy with minimal irritation in patients with melasma and PIH.[15]

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