Benefits of Using a Hydroquinone/Tretinoin Skin Care System in Patients Undergoing Intense Pulsed Light Therapy for Photorejuvenation: A Placebo-Controlled Study

Katrina E. Woodhall MD, Mitchel P. Goldman MD, Michael H. Gold MD, Julie Biron

ABSTRACT

A hydroquinone/tretinoin (HQ/tret) skin care system specifically designed for use in conjunction with non-surgical facial rejuvenation procedures has recently become available. This system is designed to condition the skin pre-procedure, and enhance the quality of the skin post-procedure. The new system uses a four-step process for improving and restoring overall skin quality through the application of cleanser, toner, 4% hydroquinone, exfoliant, tretinoin and sunscreen with a sun protection factor (SPF) 35. The first step in the process is skin preparation (using the cleanser and toner), the second step is skin correction (using hydroquinone and the exfoliant), the third step is skin stimulation (using tretinoin), and the fourth step is skin protection (using the sunscreen).

Collectively, the components of the HQ/tret system would be expected to offer improvements in various aspects of photo-damage (hyperpigmentation, fines lines and wrinkles and skin texture), as well as in acne. Intense pulsed light (IPL) therapy offers improvements in telangiectasias in addition to hyperpigmentation, fine lines and wrinkles, skin texture and erythema. Although both treatment options are effective against some of the same manifestations of photodamage, the mechanisms by which they achieve these benefits are thought to be different. As a result, their combined use may offer greater improvements in photodamage than either treatment alone. In a large-scale experience trial, pre-conditioning with the HQ/tret system alone resulted in good or excellent improvement in overall skin quality in 34% of patients who were about to receive IPL treatment. After IPL treatment and post-conditioning with the HQ/tret system, this proportion increased to 89%.

Presented here are the results of a study quantifying the clinical effects of using the HQ/tret system adjunctively with IPL.

INTRODUCTION

A hydroquinone/tretinoin (HQ/tret) skin care system specifically designed for use in conjunction with non-surgical facial rejuvenation procedures has recently become available. This system is designed to condition the skin pre-procedure, and enhance the quality of the skin post-procedure. The new system uses a four-step process for improving and restoring overall skin quality through the application of cleanser, toner, 4% hydroquinone, exfoliant, tretinoin and sunscreen with a sun protection factor (SPF) 35. The first step in the process is skin preparation (using the cleanser and toner), the second step is skin correction (using hydroquinone and the exfoliant), the third step is skin stimulation (using tretinoin), and the fourth step is skin protection (using the sunscreen).

Methods

Patients

Patients were eligible to enroll in this observer-masked, randomized, placebo-controlled study if they had moderate-to-severe facial wrinkling of the skin in the eye and lip area and were planning to undergo IPL treatment. They were also required to be 35–65 years of age with Fitzpatrick skin type I–IV.

The main exclusion criteria were: use of a non-study tretinoin product in the preceding three months or during the study; use of a systemic steroid in the preceding six months or during the study; use of a systemic retinoid in the preceding two years; any facial skin condition that might interfere with diagnosis or evaluations; and recent excessive exposure to ultraviolet light.

Washout periods were: seven days for topical products containing alpha hydroxy acids, retinoic acid, retinol, salicylic acid, or vitamins C or D (or derivatives of); 30 days for investigational drugs and for facial microdermabrasion treatment; three months for non-ablative laser, light, and radiofrequency treatment; and six months for facial dermabrasion, ablative laser treatment, and the injection of botulinum toxin type A or dermal fillers.

METHODS

Patients

Patients were eligible to enroll in this observer-masked, randomized, placebo-controlled study if they had moderate-to-severe wrinkling of the skin around the eyes and lips and were planning to undergo IPL treatment. They were also required to be 35–65 years of age with Fitzpatrick skin type I–IV.

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Treatment regimen
Patients were randomly assigned to use either a 4% hydroquinone/0.05% tretinoin skin care system or a placebo regimen, each day for 90 days. All patients also received IPL therapy on days 30 and 60. The 4% hydroquinone/0.05% tretinoin skin care system involved a morning application of cleanser, toner, hydroquinone, exfoliant, and sunscreen, and an evening application of cleanser, toner, hydroquinone and tretinoin cream. The placebo regimen involved a morning application of cleanser, moisturizer and sunscreen, and an evening application of cleanser and moisturizer.

Patients were instructed to avoid using any non-study lotions, creams, or medicated powders or solutions on their face during the study.

Outcome Measures
Evaluations were performed at baseline and at days 30, 60 and 90. The physicians evaluated the patients in terms of overall improvement in their facial skin and the degree of hyperpigmentation, laxity, telangiectasia, tactile roughness, fine lines/wrinkles, erythema, peeling, burning and dryness (Table 1). In addition, patients rated their overall improvement in facial appearance; facial skin texture; satisfaction with facial appearance; and satisfaction with treatment regimen (Table 1).

Statistical Analyses
The estimation of sample size assumed a two-sided alpha level of 0.05, power of 80%, and a drop-out rate of 10%. Data were analyzed on an intent-to-treat basis (i.e., including all randomized subjects with at least one follow-up visit). All tests were two-sided and interpreted at a 5% significance level. Between-group differences in categorical data were analyzed using a chi-square test or Fisher’s exact test.

RESULTS
Patients
Of 36 patients enrolled, 35 (97%) completed and one was lost to follow-up. They ranged in age from 35–54 years old, and the majority were female (94%), Caucasian (89%) and of Fitzpatrick skin type III (64%).

There was a significant between-group difference in the oiliness/dryness of the patients’ skin at baseline. This appeared to be because of differing numbers of enrollees with normal skin (0 in the HQ/tret system group versus 4 in the placebo + IPL group) and normal to dry skin (7 in the HQ/tret system group versus 1 in the placebo + IPL group).

Efficacy
Physician ratings of overall improvement in facial skin were significantly superior with the HQ/tret system + IPL compared with placebo + IPL at days 30, 60, and 90 (P≤0.05). At day 90, ≥75% overall improvement was reported in 72% of patients receiving the HQ/tret system + IPL and 19% of patients receiving placebo + IPL (Figures 1 and 2).

Levels of hyperpigmentation were significantly lower with the HQ/tret system + IPL than with placebo + IPL at days 30, 60, and 90 (Table 2).
and 90 ($P \leq 0.05$) (Figure 3). Mean scores showed a greater decline between baseline and day 90 with the HQ/tret system + IPL (from 2.8–1.4) than with placebo + IPL (from 2.8–2.1).

The degree of laxity was also significantly lower with the HQ/tret system + IPL than with placebo + IPL at day 90 ($P \leq 0.005$) (Figure 4). Similarly, mean scores showed a greater decline between baseline and day 90 with the HQ/tret system + IPL (from 2.2–1.6) than with placebo + IPL (from 2.2–2.1).

Levels of telangiectasia were not significantly different between the two groups (Figure 5). Nevertheless, mean scores showed a greater decline between baseline and day 90 with the HQ/tret system + IPL (from 1.9–1.4) than with placebo + IPL (from 2.0–1.9 with placebo). Improvements in tactile roughness and fine lines/wrinkles were comparable in both groups.

Between baseline and day 90, mean scores for tactile roughness declined from 2.2 to 1.0 with the HQ/tret system + IPL, and from 2.3 to 1.0 with placebo + IPL. Over the same period, mean scores for fine lines/wrinkles declined from 2.6 to 1.9 with the HQ/tret system + IPL, and from 2.6 to 2.1 with placebo + IPL (Figure 6).

### Patient Satisfaction

Patient ratings were significantly more favorable in the HQ/tret system + IPL group than the placebo + IPL group ($P \leq 0.05$ at days 30, 60 and 90 for all four patient ratings). At day 90, patient ratings revealed that: 72% versus 19% indicated that they had achieved an improvement of at least 75% in their facial appearance; 89% versus 50% thought their skin was smoother or much smoother than at baseline; 83% versus 56% were satisfied or very satisfied with their facial appearance (Figure 7); and 94% versus 56% were satisfied or very satisfied with their treatment regimen.

### Tolerability

There were no significant between-group differences in erythema with mean scores declining from 1.9 at baseline to 1.6 at baseline in both groups. Burning and peeling were transiently significantly greater with the HQ/tret system + IPL than with placebo + IPL at day 30 (resolving gradually thereafter). However, mean levels were less than trace for burning, and less than mild for peeling, throughout the study.

Mean levels of dryness were less than mild throughout the study in both groups. In the HQ/tret system + IPL group, dryness was less than mild throughout the study, with mean scores declining from 2.6 at baseline to 2.1 at day 90.

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**Table 1.**

<table>
<thead>
<tr>
<th>Scales Used For Outcome Measures</th>
<th>Physician Ratings</th>
<th>Patient Ratings</th>
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</thead>
<tbody>
<tr>
<td><strong>Improvement in facial skin</strong></td>
<td>Hyperpigmentation, laxity, telangiectasia, tactile roughness, fine lines/wrinkles, erythema, and peeling</td>
<td>Burning and dryness</td>
</tr>
<tr>
<td>100% (Complete)</td>
<td>None-normal</td>
<td>None-normal, no discomfort</td>
</tr>
<tr>
<td>~75% (Very noticeable)</td>
<td>Trace–barely visible and localized</td>
<td>Trace–an awareness, but no discomfort and no intervention required</td>
</tr>
<tr>
<td>~50% (Noticeable)</td>
<td>Somewhat visible and diffuse</td>
<td>Mild–a noticeable discomfort that causes intermittent awareness</td>
</tr>
<tr>
<td>~25% (Slightly noticeable)</td>
<td>Visible and diffuse</td>
<td>Moderate–a noticeable discomfort that causes continuous awareness</td>
</tr>
<tr>
<td>No change</td>
<td>Extremely visible and dense</td>
<td>Severe–a definite continuous discomfort that interferes with normal daily activities</td>
</tr>
<tr>
<td>Worse</td>
<td>—</td>
<td>—</td>
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D I S C U S S I O N

The results of this study demonstrate that the adjunctive use of the HQ/tret system with IPL treatment offers significantly greater overall improvements in facial skin—and significantly greater reductions in hyperpigmentation and laxity—than does placebo + IPL treatment. This illustrates the benefit of combining two complementary treatment modalities with different mechanisms of action.

The lack of a significant additive effect against telangiectasias with the adjunctive use of the HQ/tret system is not unexpected as improvements in telangiectasias might be anticipated with IPL treatment but not with hydroquinone or tretinoin. Also, the lack of additive improvements in fine lines/wrinkles may be due to insufficient time for the effects of tretinoin to become apparent as reductions in fine wrinkling may often not be evident for at least four months. Furthermore, it would be even more unlikely for any difference to be apparent within the timeframe of this study given the background improvement due to the IPL treatments at days 30 and 60. This would diminish the ability to detect any potential additive improvement with tretinoin over and above that attributable to IPL treatment.

There are few publications describing the use of the HQ/tret system in combination with other treatment modalities. However, one report involving more than 1,000 patients has detailed the clinical effects of using the HQ/tret system in combination with a range of other treatment options (including IPL, botulinum toxin, type A, fillers, non-ablative and ablative lasers, non-ablative and ablative chemical peels, microdermabrasion, and surgery). Among the 78 patients using the HQ/tret system in conjunction with IPL treatment, the proportion achieving good or excellent improvement in overall skin quality was 31% and 3%, respectively, after pre-conditioning with the HQ/tret system alone and this increased to 51% and 38%, respectively, after subsequent IPL treatment and post-conditioning with the HQ/tret system.

The results from the current study are in agreement with findings from other studies. Results from an earlier analysis evaluating the effect of IPL on facial solar lentigines using reflectance-mode confocal microscopy, optical coherence tomography, and transmission electron microscopy, suggest that the adjunctive use of hydroquinone could enhance or prolong the improvement in hyperpigmentation achieved with IPL. The authors of this report concluded that IPL treatment removes dense melanosomes in the epidermal basal layer but that a suppressive drug such as hydroquinone is necessary to suppress the remaining active melanocytes. Tretinoin is also known to reduce hyperpigmentation although its use in combination with

IPL treatment is not well described. Tretinoin and IPL treatment have each been reported to reduce laxity whereas, to our knowledge, hydroquinone has not. We therefore conclude that, when the HQ/tret system is used adjunctively with IPL treat-
ment, the enhanced reductions in laxity are likely attributable to tretinoin and the enhanced reductions in hyperpigmentation are likely attributable to both hydroquinone and tretinoin.

Although the mean levels of burning and peeling were transiently significantly greater with the HQ/tret system + IPL than with placebo + IPL, the patient satisfaction data suggest that these were not a concern to the patients in practice. Patient satisfaction data were significantly more favorable with the HQ/tret system + IPL than with placebo + IPL at day 30 (when the between-group differences in tolerability parameters were greatest), as well as at day 60 and day 90 (P<0.05).

Further research, with monitoring continuing beyond 90 days, would be of interest in order to better understand the role that the HQ/tret system can play in maintaining the improvements attained with IPL treatment.

CONCLUSION

Adjunctive use of the HQ/tret system enhances the overall improvements in facial skin achieved with IPL therapy alone—resulting in significantly lower levels of hyperpigmentation and laxity, and significantly greater levels of overall improvement and patient satisfaction. Use of the HQ/tret system in combination with IPL treatment was generally well tolerated with mean levels of dryness, peeling and burning remaining less than mild throughout the study.

DISCLOSURES

This study was conducted with a research grant from Obagi Medical Products, Inc. Dr. Goldman is a consultant for Obagi Medical Products, Inc., and Dr. Gold is an investigator and consultant for Obagi Medical Products, Inc.

REFERENCES


**ADDRESS FOR CORRESPONDENCE**

Mitchel P. Goldman, MD
Medical Director
La Jolla Spa MD
7630 Fay Avenue
La Jolla, CA 92037
Phone: .................................................................(858) 459-7011
E-mail: .................................................................mgderm@aol.com

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