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"Hydroquinone-Free Skincare Treatment for Hyperpigmented Facial Skin: An Effective, Well-Tolerated, and Safe Approach for Japanese Patients"

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1. Introduction

Facial skin hyperpigmentation disorders such as post-inflammatory hyperpigmentation (PIH), solar lentigines, and melasma are frequently observed in Asian patients with Fitzpatrick skin types III–IV [1–3]. Management of hyperpigmentation requires a multipronged approach in the Asian population, where fairer skin is often culturally desirable [4]. For example, in Japan, patients self-reporting facial hyperpigmentation disorders completed a quality of life (QoL) questionnaire to better understand the psychological and social impact of these concerns [4]. Compared to a control group without facial hyperpigmentation, the results indicated a significant negative effect on QoL [4]. Physical appearance has been found to be a key determinant of personal well-being [5]. As such, patients increasingly turn to healthcare providers to guide them toward evidence-based, effective, and well-tolerated treatment strategies that not only address visible pigmentation but also support long-term skin health and confidence.

One of the most frequently used treatments for the management of hyperpigmentation is hydroquinone, a topical bleaching agent [3,6]. Interestingly, hydroquinone was documented to have selective cytotoxic effects on melanocytes [7,8]. While effective, long-term use of hydroquinone can cause adverse effects such as irritation, allergic reactions, confetti-like depigmentation, and exogenous ochronosis [8,9]. Due to these risks, the FDA reclassified hydroquinone, originally found over the counter (OTC), as prescription-only in 2020 [10]. Additionally, the EU's Annex II (entry 1339) has listed hydroquinone as a substance prohibited for use in cosmetic products [11]. These limitations highlight the need for alternative depigmenting agents and procedures with more favorable safety profiles, particularly in Japanese and Asian populations.

While chemical peels, intense pulsed light (IPL), and fractional skin resurfacing have shown success in treating hyperpigmentation, these procedures typically require multiple sessions, involve downtime, and carry a risk of PIH, and additional factors that may not be ideal for many Japanese patients [2, 12]. In contrast, topical physician-dispensed skincare offers a non-invasive alternative that may be better suited for this population [13,14]. Tetrahexyldecyl (THD) ascorbate, a skin-mimicking, lipid-soluble form of vitamin C, allows for skin-neutral pH formulations and provides superior skin penetration compared to L-ascorbic acid to assist in the effective inhibition of tyrosinase in the melanogenesis process [15,16]. Retinol is effective in accelerating epidermal cell turnover, dispersing melanin granules, and inhibiting tyrosinase transcription, mechanisms that collectively reduce melanin accumulation

in the skin [17]. The combination of topical vitamin C and vitamin A has demonstrated promising results in improving photodamaged and hyperpigmented skin [18-22].

This retrospective review evaluates two years of clinical data assessing the efficacy of a medical-grade skincare regimen containing vitamin C and vitamin A with prescription strength 0.1% tretinoin (TRET) in the treatment of moderate to severe facial hyperpigmentation. The study population consisted of Japanese patients aged 30 to 65 years with Fitzpatrick Skin Types II–IV. The underlying hypothesis suggests that a regimen incorporating pharmacologically active concentrations of vitamin C and vitamin A can effectively target pigmentation while supporting overall skin rejuvenation through a more comprehensive, balanced therapeutic approach.

2. Materials and Methods

Patients underwent a two-phase topical skincare regimen, “XT Protocol”. In Phase I, approximately 4 months in length, patients followed a morning and evening skincare routine. Immediately after facial cleansing, a non-alcohol-based soothing facial toner (SFT), a vitamin C serum (VCS) formulated with 30% THD ascorbate and patent-pending antioxidant technology, and an anti-aging daily moisturizer (ADM) formulated with peptides and microbiome technology targeting the dermal-epidermal junction were applied sequentially to the face. For the morning routine, sunscreen was applied as the last step. In the evening, dependent on Phase I or Phase II, the routine was controlled to ensure adherence and minimal irritation.

In the first 2 weeks of Phase I, the ADM and TRET were mixed in a 1:0.5 or 1:1 ratio to create a “smoothie”. The ADM/TRET smoothie was applied every evening or 2 to 3 times a week depending on the patient’s tolerability. After the 2-week acclimation period, a return to the clinic to review results was required before proceeding with the XT protocol. At week 3, the ADM and TRET are applied separately to the face, rather than mixed, ADM was the last step of the application to assist in keeping the skin moisturized. TRET application was every evening until completion of this phase. Once Phase I was completed, patients moved into Phase II. In Phase II, the TRET topical was replaced with a 1.0% or 0.5% encapsulated retinol serum formulated with bakuchiol (RSB).

Clinical outcomes, including review of 3D facial photography with QuantifiCare LifeViz® (QuantifiCare, France), clinical photography with re-Beau2 (JMEC Co., Ltd, Japan) under standard and UV light, tolerability assessments, and adverse events, were included in this two-year retrospective review. ImageJ software (National Institutes of Health, MD) was utilized to objectively measure pixel intensity in the QuantifiCare and re-Beau2 photographs of the patient’s cheeks to determine percent (%) improvement in skin tone evenness from baseline at post-baseline timepoints [22]. A maximum pixel intensity of 255 represents complete skin tone evenness (brightness) and a pixel intensity of 140 or less represents maximum skin tone evenness.

3. Results

In Phase I, mild peeling was observed in the majority of patients as they acclimated to 0.1% TRET topical. No patient discontinued product use during either Phase I or Phase II. No adverse events were reported throughout the two-year review period. To ensure tolerability with the 30% VCS, a small amount of the product was placed on inner forearm to see if any irritation or reaction develops. Additionally, for Phase II, patients were either shifted to the RSB 0.5% or 1.0% depending on how well they tolerated the 0.1% TRET product.

Visible improvements in hyperpigmentation, skin radiance, and skin tone evenness were evident during Phase I. In Figure 1, a 59-year-old patient that started the XT protocol in the summer showed a 15% improvement in skin tone evenness in right cheek area after completing Phase 1.



Figure 1. Clinical photography captured with QuantifiCare LifeViz® of a 59-year-old male patient with Fitzpatrick Skin Type III and moderate global hyperpigmentation. Baseline image prior to treatment (A) and follow-up image after 4 months, demonstrating visible improvement in overall skin tone and reduction in hyperpigmentation (B).

Clinical photography captured under UV light demonstrated significant improvement in overall hyperpigmentation and skin health. In Figure 2, a 51-year old female patient with moderate to severe hyperpigmentation saw significant reduction in pigment intensity, area, and size after completing Phase I and 1 month into Phase II of the XT protocol.

Improvements were evident in the left forehead, under-eye area and cheek region. After 5 months on the XT protocol, an 11% improvement in skin tone evenness was determined, thus indicating a reduction in hyperpigmentation.

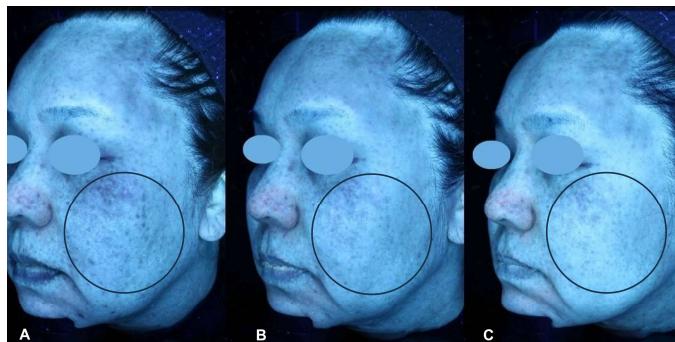


Figure 2. Clinical photography captured with re-Beau2 under UV light of a female patient aged 51 years with Fitzpatrick Skin Type III and with moderate to severe hyperpigmentation. Baseline before treatment (A) post-baseline at 3 months within Phase I, 3% improvement (B) post-baseline after 1 month in Phase II, 5 months from baseline, 11% improvement (C).

Additionally, patients within the age group between 40-50's saw intensified improvement and management of their hyperpigmentation after incorporating oral tranexamic acid during Phase I of the XT protocol. There were no indicated risks seen with this incorporation. In Figure 3, a 48-years of age female patient with moderate hyperpigmentation had a 11% improvement in skin tone evenness after 3 months of starting XT protocol and incorporated oral tranexamic acid after 2 months into Phase I.

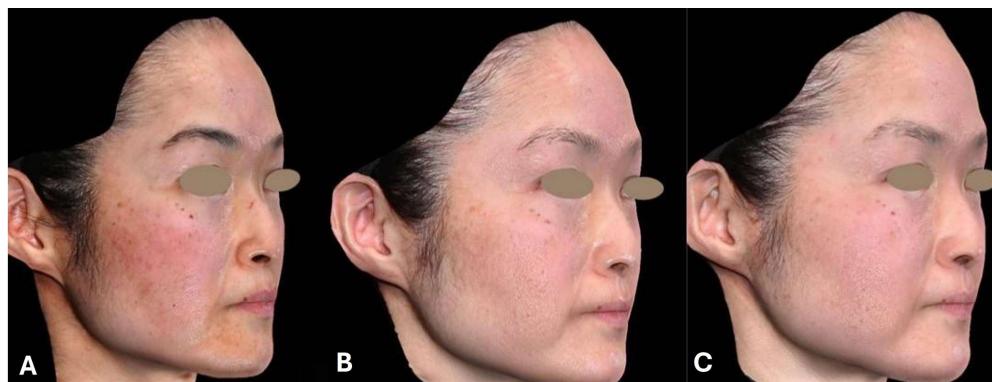


Figure 3. Clinical photography captured with QuantifiCare LifeViz® of a female patient aged 48 years with Fitzpatrick Skin Type III and with moderate hyperpigmentation. Baseline image before treatment (A) post-baseline at 2 months within Phase I (B) post-baseline after 3 months within Phase I and oral tranexamic acid (C).

Table 1, summarizes the percent improvement in skin tone evenness across Phase I and Phase II. As can be seen in the table, some patients incorporated tranexamic acid into the XT protocol to have better control of their melasma. In particular, one subject transitioned to the 0.5% RSB and saw some regression in improvement. However, this patient did not have complaints and was content with her results.

Table 1. Summary of percent (%) improvement in skin tone evenness across reviewed patients on the XT Protocol. Calculations were made with Image by measuring pixel intensity.

Patient (Age, Sex)	Phase I	Phase II	Details
46-years, Female	4%	5%	Oral tranexamic acid started in Phase I
48-years, Female	11%	Not available	Oral tranexamic acid month 2 of Phase I
51-years, Female	3%	11%	Phase I ratio ADM:TRET 1:0.5. Phase II transitioned to 1.0% RSB (every other evening of application)
52-years, Female	8%	5%	Phase I ratio ADM:TRET 1:1. Phase II transitioned to 0.5% RSB

Also noted, this two-phase regimen was prescribed for patients that can no longer be on hydroquinone and those that have had experience with physician-dispensed skincare. Patients on the XT protocol had the following feedback:

- Skin peeling is minimal and the treatment is easy to continue
- Application of the products in the XT protocol makes the skin look beautiful
- While deep pigmentation may eventually require laser treatment, the skin's texture improves, the tone brightens, and fine lines are visibly reduced
- The simple step-by-step process in the XT protocol is easy to remember

Overall patients were satisfied and were willing to continue using the Phase II skincare regimen. Since only a part of the skincare routine needs to be changed, patients appreciated

that they can continue using most of their usual products even after the treatment, without waste.

4. Discussion

Facial hyperpigmentation remains a prevalent and challenging concern, with patients consistently seeking safe and effective treatment options, globally. In the United States, healthcare providers (HCPs) commonly recommend the intermittent use of hydroquinone to mitigate safety concerns associated with prolonged use [12-14]. Typically, patients are advised to cycle off hydroquinone after 3 months and transition to a physician-dispensed depigmenting skincare regimen that includes ingredients such as vitamin C, peptides, microbiome technology, and vitamin A to maintain results and support skin health. In Japan, hydroquinone can be sold over the counter at concentrations up to 2%. For concentrations above this threshold, a prescription is required. In response to both clinical demand and safety considerations, the XT protocol was developed as a two-phase treatment regimen for the treatment of hyperpigmentation in Japan.

The XT protocol combines high efficacy skincare with prescription-strength 0.1% tretinoin (retinoic acid) to provide a hydroquinone-free solution for patients seeking reliable correction and protection from facial hyperpigmentation. Importantly, the XT protocol is designed to minimize the risk of common adverse effects associated with hydroquinone, such as redness, inflammation, and allergic reactions; concerns that have been notably observed in populations such as those in Japan and can be relevant globally.

The XT protocol leverages the synergistic effects of three key components, the VCS, ADM, and RSB, offering HCPs an effective alternative regimen. In Phase I, patients followed a morning and evening skincare routine for 4 months, resulting in visible correction of facial hyperpigmentation. Phase II focused on ongoing maintenance and improvement. Patients reported high adherence to the skincare routine and expressed satisfaction with the experience, even after discontinuing TRET. For those experiencing mild regression post-Phase I, adjunctive treatments such as intense pulsed light (IPL), laser resurfacing, and oral tranexamic acid were introduced in Phase II to enhance and accelerate pigment control.

Designed to be implemented year-round, the XT protocol offers customizable solutions suitable for both women and men, making it a versatile tool in the management of facial hyperpigmentation.

5. Conclusion

Due to long-standing safety concerns associated with continuous hydroquinone use, HCPs recommend an intermittent approach. The XT protocol offers a clinically validated, hydroquinone-free alternative that enables both effective correction and sustained management of facial hyperpigmentation. By integrating prescription-strength tretinoin with physician-dispensed skincare, the XT protocol empowers providers with a comprehensive solution—designed not only to treat but also maintain healthy, even-toned skin over time.

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