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Combination treatment algorithm for pigmentary disorders of the face: A prospective observational study in Asian patients

Chikara Takekawa[a,b], **Takeshi Fukumoto**[c,d,*], **Goichi Haraoka**[a], **Hiroto Terashi**[e]

[a] *Department of Aesthetic Surgery, Kobe University Hospital, Kobe, Japan*
[b] *Department of Plastic and Aesthetic Surgery, Koyama Clinic, Kobe, Japan*
[c] *Gene Expression and Regulation Program, The Wistar Institute, Philadelphia, PA, United States*
[d] *Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan*
[e] *Department of Plastic Surgery, Kobe University Hospital, Kobe, Japan*

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Carbon dioxide laser

Summary
Background: Most patients with facial pigmentary disorders have multiple disorders. However, there is no definitive treatment algorithm improving various pigmentary disorders simultaneously.
Objectives: To investigate the clinical efficacy and safety of the combination of the Q-switched alexandrite and the carbon dioxide lasers with ZO SKIN HEALTH® for facial pigmentary disorders.
Patients/methods: This prospective observational study enrolled 251 patients with at least one facial pigmentary disorder. We assessed treatment efficacy and investigated which disorders were most responsive to combination treatment and the relationship between doctors' skills, outcomes, and dropout rates.
Results: There were 246 patients with lentigo senilis, 186 with moles, 79 with melasma, 53 with seborrheic keratosis, 17 with acquired dermal melanocytosis (ADM), and 16 with freckles. Overall, 227 patients completed treatment. Post-treatment outcomes were excellent in 97,

Abbreviations: ADM, acquired dermal melanocytosis; CO_2, carbon dioxide; LS, lentigo senilis; RA, retinoic acid; TA, tranexamic acid.

* Corresponding author at: Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan.
E-mail address: fuku@med.kobe-u.ac.jp (T. Fukumoto).

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good in 113, fair in 17, and poor in 0 patients. Freckles were the most responsive, and ADM was the least responsive. Patient withdrawal and treatment outcomes did not differ significantly based on the doctors' skills. Overall, 3.2% of patients had adverse events.

Conclusions:: Our combination algorithm improved several pigmentary disorders of the face simultaneously, regardless of the doctors' proficiency level.

Introduction

There are many acquired pigmentary disorders of the face, such as lentigo senilis (LS), melasma, acquired dermal melanocytosis (ADM), freckles, moles, and seborrheic keratosis (SK), all of which can affect patients' quality of life. Even if biologically benign, these disorders represent some of the most common reasons for consulting dermatological or cosmetic clinicians.[1-9] Several treatments, including laser therapies, such as the Q-switched alexandrite and the carbon dioxide (CO_2) lasers, topical ointment therapies such as vitamin C derivatives, hydroquinone, and retinoic acid (RA), and oral medicines such as tranexamic acid (TA), vitamin C, and vitamin E, are available for these pigmentary disorders.[1-7,9-11] Although most patients present with several types of pigmentary disorders on their faces, there is not one definitive treatment algorithm that can cure all of these pigmentary disorders simultaneously.

For example, LS is a common condition giving rise to pigmented lesions of various sizes, mostly seen on sun-exposed sites, such as the face, of elderly persons.[1,2,11] There are several treatment options for LS, including laser therapy or topical ointment therapies, such as vitamin C derivatives, hydroquinone, or RA.[2] Melasma is symmetrical hypermelanosis commonly found on the cheeks and foreheads of women, especially after adolescence, but its pathogenesis is not clearly understood.[1,3,4] Melasma can be treated with various therapies, and the use of ointments, chemical peels, laser toning treatments, and oral medicines such as TA, vitamin C, and vitamin E has been reported.[3,5-7] ADM is a symmetrical grayish disorder with dermal melanocytes that spread. They frequently exist on the cheeks, foreheads, and noses, and the pathogenesis is not well understood.[8] Although no appropriate treatment for ADM has been suggested, laser therapy has been reported to be effective.[8] Freckles are 1–5 mm melanocytic disorders commonly present on the cheeks and noses that can be treated with topical hydroquinone or laser therapy.[12-14] Moles and SK are indications for CO_2 laser treatment.[10]

ZO SKIN HEALTH® (ZO®) is a treatment developed by Obagi Cosmeceuticals LLC (Long Beach, CA, USA), which comprises a combination therapy of 4% hydroquinone containing creams (Milamin® and Miramix®) and RA and is administered in an 18-week program.

ZO® can improve LS, melasma, and freckles, which are pigmentary disorders in the epidermis, but it cannot improve moles and SK (benign skin tumors) and ADM (a pigmentary disorder in the dermis). Therefore, the CO_2 laser can be used to ablate the skin for moles and SK, and the Q-switched alexandrite laser can be used for ADM to destroy melanin in the dermis. In addition, the Q-switched alexandrite laser can be effective for LS and freckles. With regard to melasma, the addition of oral medicines can be more effective than ZO® treatment alone.[5-7] That is, we incorporated the Q-switched alexandrite laser and the CO_2 laser into the 18-week ZO® program to create a combination treatment algorithm that can improve a wide variety of pigmentary disorders efficiently and simultaneously (Table 1). This study aimed to investigate the clinical efficacy and safety of the combined treatment algorithm of the Q-switched alexandrite and CO_2 lasers and ZO®. It would be great to obtain consistently effective, safe, and stable results of treatment based on this algorithm regardless of doctors' proficiency level, which could be beneficial for both patients and clinicians.

Patients and methods

Patients and study design

This was a prospective observational study of 251 patients with at least one pigmentary disorder on their face who were seen between June 2014 and March 2018 at the Department of Plastic and Aesthetic Surgery of the Koyama Clinic. All patients provided written informed consent. The protocol was approved by the ethics committee of the Koyama Clinic.

Pigmentary disorder types were diagnosed based on previous studies by a medical interview and visual inspection by three investigators with plastic surgery expert licenses, and classified into LS, melasma, ADM, freckles, moles, and SK.[1-14]

Because various hypersensitivities have been reported for hydroquinone, all patients first applied Milamin® and Miramix® on their cheeks for 5 days to check for reactions, such as irritation, redness, or itching.[14-16] In patients without any hypersensitivities, the ZO® treatment with 0.1% RA was initiated. Patients who showed hypersensitivities were treated with a cream (Buraitalive®) containing brightonil instead of hydroquinone.

The treatment plans differed depending on the presence of melasma. In patients with melasma, ZO® treatment was initiated in combination with 500 mg of TA (twice a day orally), 1 g of vitamin C (twice a day orally), and 50 mg of vitamin E (once a day orally).[6,7] If melasma improved in the 6th week, Q-switched alexandrite laser therapy (7.5 J/cm^2) was performed for ADM, LS, and freckles. If melasma was still present in the 6th week, Q-switched alexandrite laser therapy (7.5 J/cm^2) was only performed for ADM, LS, and freckles on the sites that did not overlap with melasma. In patients with no melasma diagnosis, Q-switched alexandrite laser therapy (7.5 J/cm^2) was performed for ADM, LS, and freckles in the 6th week. In patients with moles and SK, CO_2

Table 1 Indications for the combination treatment algorithm.

	ZO	Q-switched alexandrite laser	CO_2 laser	Oral medicines
LS	○			
Melasma	○			○
ADM		○		
Freckles	○	○		
Moles			○	
SK			○	

Lentigo senilis (LS), Acquired dermal melanocytosis (ADM), Seborrheic keratosis (SK) Oral medicines; Tranexamic acid + Vitamin *C* + Vitamin E.

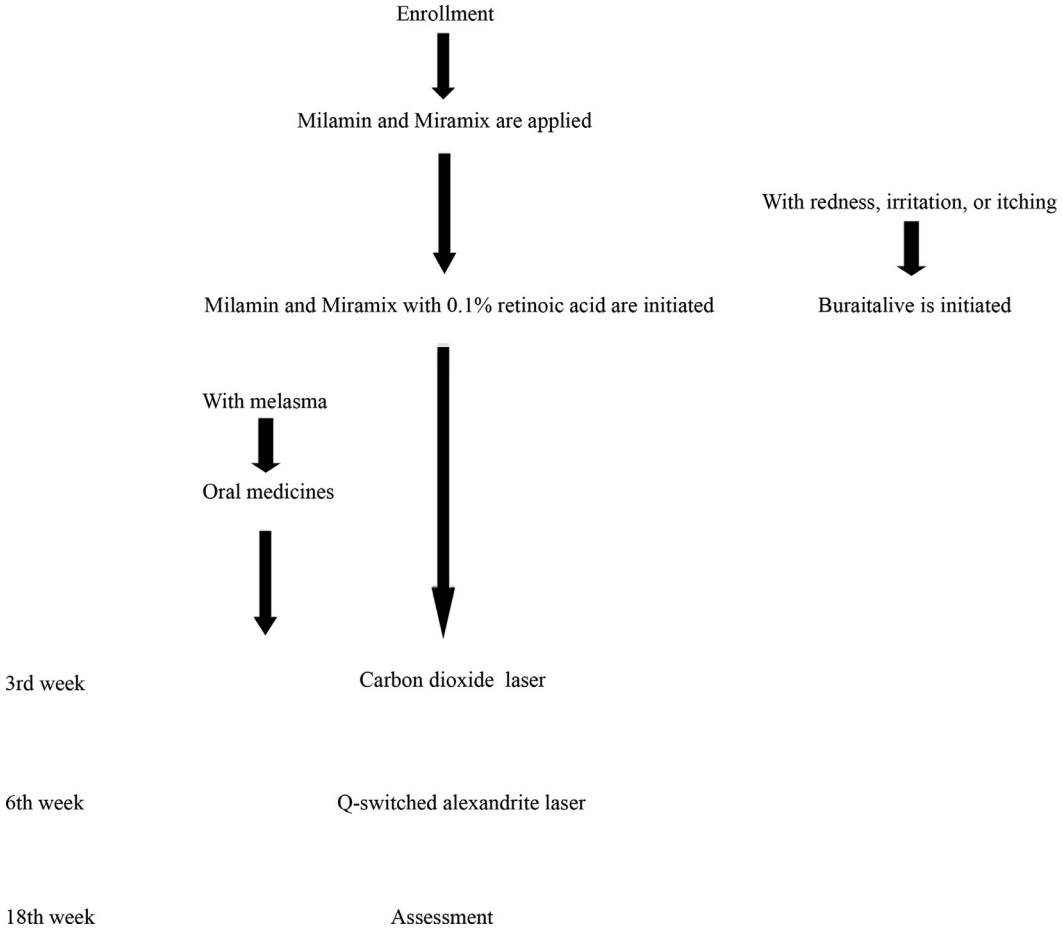

Figure 1 Flowchart of the treatment algorithm.

laser therapy was performed in the 3rd week. The RA dosage was gradually decreased beginning in the 12th week to suppress redness and skin scaling by the 18th week (Figure 1). We excluded patients who had received long-term treatment with any medication and patients with any other skin disease on their face. The use of other cosmetic agents and strong sun exposure were prohibited during the study.

Primary outcome (efficacy assessment)

The treatment efficacy was assessed by comparing an image taken at the first visit to an image taken in the 18th week. Three investigators with plastic surgery expert licenses assessed the images independently. The treatment efficacy was classified as follows: 4 points (excellent: pigmentary disorders had disappeared), 3 points (good: pigmentary disorders had almost disappeared), 2 points (fair: pigmentary disorders had not changed), and 1 point (poor: pigmentary disorders had become worse). The scores from all three investigators were added, and a score of 12 points represented a full treatment effect.

Secondary outcome (statistical analyses)

We sought to investigate what type of disease was most responsive to this combination treatment using a *t*-test. Moles

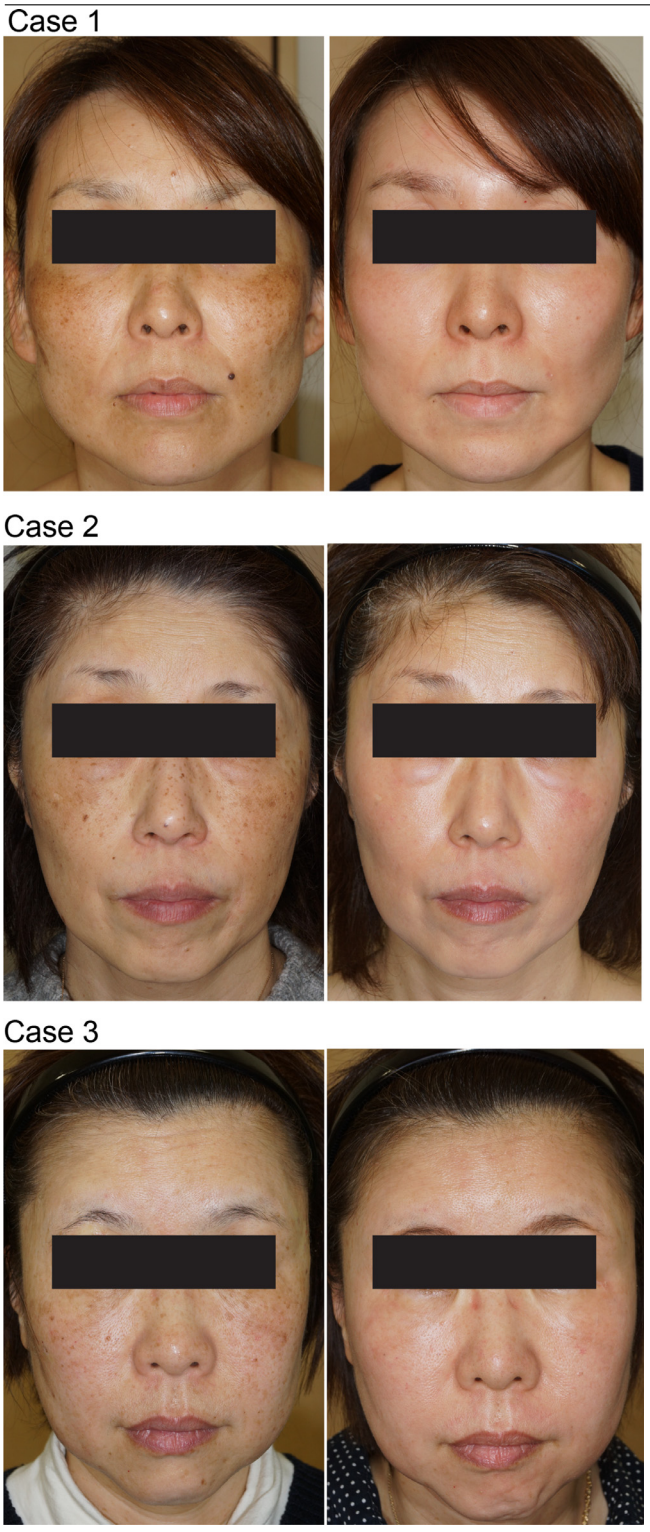

Figure 2 Pre- and post-treatment images. Pre-treatment (left) and post-treatment (right) images of Cases 1, 2, and 3.

were excluded because some patients consider moles to be aesthetically attractive. As LS was observed in almost all patients (246/251 patients), we used a *t*-test to compare (1) the mean score of patients with LS alone and the mean score of patients with both melasma and LS, (2) the mean score of patients with both SK and LS, (3) the mean score of patients with both ADM and LS, and (4) the mean score of patients with freckles and LS. Furthermore, we sought to examine the associations between the skill level of the doctor, the treatment effect, and the dropout rate. We used analysis of variance (ANOVA) to assess the year-by-year change in treatment effect and a chi-square test to assess the year-by-year change in treatment dropout numbers.

Results

A total of 251 patients (3 males and 248 females) were enrolled. All patients were Japanese, and the mean age was 50.8 years. One patient was 20–29 years old, 37 were 30–39, 91 were 40–49, 63 were 50–59, 46 were 60–69, 11 were 70–79, and 2 were 80–89. Moreover, 3 of the 251 patients used Buraitalive® throughout the treatment course because of hypersensitivities to hydroquinone at the first check. The enrolled disorders were as follows: 246 patients had LS, 186 had moles, 79 had melasma, 53 had SK, 17 had ADM, and 16 patients had freckles. Twenty-four patients dropped out of treatment, and the remaining 227 patients completed the treatment course (Supplementary Table 1). Ninety-seven patients showed excellent results, 113 patients showed good results, 17 patients showed fair results, and no patient showed poor results. In total, 8 (3.2%) of the 251 patients presented with adverse effects, such as irritation or redness. As mentioned above, 3 of these patients showed adverse effects at the first check and completed the treatment course using Buraitalive® instead. Five of these patients showed adverse effects during the treatment course. Of these 5 patients, 3 used Buraitalive® to complete the treatment course and 2 patients dropped out.

The mean score of the treatment efficacy for each disease was calculated as described above. The lowest to highest scores were as follows: ADM 8.60 points, LS 9.53 points, SK 10.10 points, melasma 10.15 points, and freckles 11.10 points (Table 2). The differences between each mean value were compared using a *t*-test (Table 3). The year-by-year change in the number of withdrawals did not differ significantly (chi-square test: $p>0.05$; Supplementary Table 2) nor did the year-by-year change in the treatment effect (ANOVA: $p>0.05$; Supplementary Table 3).

Case 1 (Figure 2)

A 47-year-old woman presented with LS, melasma, and moles. Given the presence of melasma, 500 mg of TA (twice a day orally), 1 g of vitamin C (twice a day orally), and 50 mg of vitamin E (once a day orally) were administered. CO_2 laser therapy was performed in the 3rd week for moles. Because the melasma had improved significantly by the 6th week, Q-switched alexandrite laser therapy was performed at the 6th week for LS. Beginning in the 12th week, the RA dosage was tapered. In the 18th week, the treatment algorithm ended with no redness or scaling. The treatment efficacy score was 12.

Table 2 Efficacy assessments.

	ADM	LS	SK	Melasma	Freckles
The mean score of treatment efficacy	8.60	9.53	10.10	10.15	11.55
Number of patients	7	19	39	56	9

Acquired dermal melanocytosis (ADM), Lentigo senilis (LS), Seborrheic keratosis (SK).

Table 3 Statistical analysis showing differences between each mean value of treatments using a *t*-test.

	LS	Melasma	SK	ADM	Freckles
LS	-	1.3	1.15	1.19	***2.85***
Melasma	1.3	-	0.14	***2.22***	***127***
SK	1.15	0.14	-	***2.18***	***2.28***
ADM	1.19	***2.22***	***2.18***	-	***3.18***
Freckles	***2.85***	***227***	***2.28***	***3.18***	-

Lentigo senilis (LS), Seborrheic keratosis (SK), Acquired dermal melanocytosis (ADM) ***Bold/Italic numbers*** are significant (*t*-test, $P<0.05$).

Case 2 (Figure 2)

A 55-year-old woman presented with LS, melasma, freckles, moles, and SK. Given the presence of melasma, 500 mg of TA (twice a day orally), 1 g of vitamin C (twice a day orally), and 50 mg of vitamin E (once a day orally) were administered. CO_2 laser therapy was performed at the 3rd week for moles and SK. Because the melasma had improved significantly by the 6th week, Q-switched alexandrite laser therapy was performed in the 6th week for LS and freckles. Beginning in the 12th week, the RA dosage was tapered. In the 18th week, the treatment algorithm ended with no redness or scaling. The treatment efficacy score was 11.

Case 3 (Figure 2)

A 51-year-old woman presented with LS, moles, and SK. No oral medications were administered because there was no melasma. Q-switched alexandrite laser therapy was performed in the 6th week for LS. Beginning in the 12th week, the RA dosage was gradually reduced. In the 18th week, the treatment algorithm ended with no redness or scaling. The treatment efficacy score was 12.

Discussion

We performed a prospective observational study to investigate whether a combination treatment algorithm of ZO®, Q-switched alexandrite laser therapy, and CO_2 laser therapy was effective for several types of pigmentary disorders simultaneously. We developed an algorithm that incorporated both Q-switched alexandrite and CO_2 lasers during the 18-week treatment course of ZO®. Both laser techniques were used because Q-switched alexandrite laser therapy is suitable for ADM, LS, and freckles, but unsuitable for melasma, while CO_2 laser therapy is indicated for moles and SK. Additionally, we incorporated oral medications, including TA, vitamin C, and vitamin E for the treatment of melasma. Our study showed the clinical efficacy and safety of this combination algorithm for several pigmentary disorders of the face.

Hydroquinone dosing is not well established, as various dosages have been reported in previous studies. The use of an incorrect dosage of hydroquinone may affect its therapeutic efficacy and contribute to adverse reactions, such as irritation.[17-22] In this study, ZO® was applied using a bottle with a pump that emits a constant volume of solution, simplifying quantification of the drug and helping avoid dosage error. At the check-up in the 1st week, the dosage already administered was checked and adjustments were made to ensure the correct dosage for the rest of the treatment course. In addition, Q-switched alexandrite and CO_2 lasers are familiar to dermatologists and plastic surgeons who treat pigmentation disorders, which made this treatment algorithm convenient for the clinicians. In the 3rd week, CO_2 laser therapy was used for the moles and SK that were not improved with ZO®. The irradiated sites were affixed with duoactive ET® until epithelialization, and the other treatments were continued. Downtime following CO_2 laser therapy was completed by the 18th week. In the 6th week, Q-switched alexandrite laser therapy was used for ADM, LS, and freckles. The application of Q-switched alexandrite laser therapy was determined by the status of melasma. The RA dosage was reduced to suppress redness and skin scaling beginning from the 12th week, and the treatment was completed by the 18th week. In total, this treatment algorithm resulted in good outcomes in more than 90% of patients at the end of the 18th week. The sequence of combined treatments is also important. That is, SK, moles, and ADM should be treated early in the treatment program because they need to be treated by laser and the downtime after laser can be completed within the 18-week treatment period. Since the cheeks and foreheads where ADM is frequently present is also the site where melasma is frequently found, and the Q-switched alexandrite laser may worsen melasma, the Q-switched alexandrite laser for ADM, LS, and freckles is used in the middle of the program after improving melasma. Another benefit of irradiating the Q-switched alexandrite laser in the middle of the treatment program is that ZO® can improve LS and freckles, leading to less shots of the Q-switched alexandrite laser. As a result, we irradiated the CO_2 laser early in the treatment program and the Q-switched alexandrite laser in the middle of the treatment program. Also both downtimes of ZO® and laser therapy can be finished simultaneously. It may be difficult to achieve consistently effective, safe, and stable results in a short period of time if each treatment is performed separately.

Based on the results of the *t*-test of the mean treatment efficacy scores for each disorder, freckles were more effectively treated than other disorders, and ADM was less effectively treated compared with all other disorders, except for LS. This may be because ADM is a dermal lesion and requires multiple irradiations by the Q-switched alexandrite laser. Although this algorithm improves both epidermal and dermal lesions, our results revealed that this algorithm can be more useful for superficial lesions (Tables 2 and 3). In particular, ADM is not cured completely within the 18-week treatment because it requires multiple irradiations, which must be communicated to the patient before starting this combination treatment.

In addition, Asians are prone to pigmentation due to laser treatment. This treatment algorithm combines RA that promotes melanin excretion in the epidermis and hydroquinone that suppresses melanin production; this minimizes pigmentation after laser treatment and makes this algorithm more meaningful. Moreover, our treatment algorithm utilizes an intensive treatment regimen that results in a short treatment course, which can maintain patients' motivation to achieve more than 90% sufficient outcomes. Furthermore, it is important to note that there were no significant differences in treatment efficacy or the numbers of patients who dropped out of treatment due to the skill of the doctors. This means that this treatment algorithm can yield consistent results regardless of doctors' skill level; this finding supports the general use of this treatment algorithm. Finally, this combination treatment can result not only in reduced pigmentation but also in skin rejuvenation and more luminous skin, making patients look younger and feel more satisfied.

This study had some limitations. First, this was a clinical prospective observational trial. A comparative study with a control group (e.g., each single treatment group) is needed to determine the differences in efficacy and establish more validated scientific evidence. Second, we did not consider cost-effectiveness. Third, although eight patients (3.2%) showed adverse effects, we could not confirm which materials caused these adverse effects because the patients did not want to undergo skin tests. In the future, we aim to investigate another algorithm to effectively maintain treatment improvements after the treatment course has ended.

Conclusion

Our treatment algorithm combined ZO® with Q-switched alexandrite and CO_2 lasers to efficiently and simultaneously improve various face pigmentary disorders. In this study, 227 patients completed the treatment algorithm and more than 90% achieved effective results. Furthermore, statistical analyses showed that this treatment algorithm can result in consistent outcomes regardless of doctors' proficiency level.

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None.

Declaration of Competing Interest

None declared.

Level of evidence

Level IV.

Author Contributions

Takekawa, Fukumoto, and Terashi were responsible for study concept and design; Takekawa and Fukumoto were involved in analysis and interpretation of data; and Takekawa, Fukumoto, Haraoka, and Terashi were mainly involved in drafting of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2020.08.131.

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