Retreatment using a dual mode of low-fluence Q-switched and long-pulse Nd:YAG laser in patients with melasma aggravation after previous therapy

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Abstract
Background: Aggravated melasma after treatment is vulnerable to stimulation, can easily deteriorate, and may be distressing without proper management.
Objective: To retrospectively assess the effectiveness and safety of combination therapy using low-fluence Q-switched neodymium-doped yttrium aluminum garnet (Nd:YAG) laser (QSNY) and long-pulse Nd:YAG laser (LPNY) (dual toning) in patients with rebound melasma.

Materials and methods: A total of 30 patients with aggravated melasma after previous therapy were treated with dual toning. A total of 10 sessions were conducted at 1-week intervals, followed by maintenance treatment. The results were evaluated using the modified Melasma Area and Severity Index (mMASI) and the physician’s global assessment (PGA) before and 2 months after completing the 10 treatment sessions.

Results: The baseline mMASI was 10.48 ± 3.64, which significantly decreased to 3.22 ± 1.45 2 months after completing the 10 treatment sessions (p < 0.001). Twenty-four patients (80%) had PGA grade 4 (76–100% improvement) and 6 patients (20%) had PGA grade 3 (51–75% improvement).

Conclusion: Dual toning may be a safe and effective salvage treatment for patients with aggravated melasma after previous treatment. LPNY may stabilize melasma activity to prevent rebound hyperpigmentation via dermal remodeling.

Key Words: Adverse events, long-pulsed Nd:YAG laser, melasma, Q-switched Nd:YAG laser, rebound hyperpigmentation,
The low-fluence 1064-nm QSNY has been widely used recently in Asia as a safe and effective treatment for melasma, referred to as laser toning (4–7). This technique involves multiple weekly treatments using multiple passes of a low-fluence, collimated beam with a large spot size and a frequency of 5–10 Hz. Recent studies on its mechanism of action suggest that melanin in melanophores was selectively destroyed while the melanin-containing cells were left intact, which results in clinical lightening of the pigment while minimizing the risk of rebound hyperpigmentation (8,9). Nonetheless, rebound hyperpigmentation has been reported after treatment with the laser toning technique, which may be associated with the excessive cumulative laser energy (10). We combined a 1064-nm LPNY with a QSNY with lower fluence than that used for conventional laser toning. Compared with conventional laser toning, this dual toning technique for melasma treatment appeared to be associated with minimal adverse events including rebound hyperpigmentation and mottled hypopigmentation (unpublished data). Although LPNY was originally used for the treatment of vascular lesions and hair removal, it can also be used for photorejuvenation (11,12). LPNY might improve the altered dermal environment observed in melasma patients through the remodeling of the vasculature and collagen structure, which stabilizes melasma activity and prevents aggravation. We retrospectively assessed the efficacy and safety of retreatment using dual toning in patients with melasma aggravation after previous treatment.

Materials and methods

Patients with aggravated melasma after previous treatment, dual toning between 2007 and 2012, were included in this study. Informed consent was obtained from all patients before treatment. All procedures were carried out in accordance with the ethical standards of the responsible committee on human experimentation and the Declaration of Helsinki of 1975, as amended in 1983. Exclusion criteria included underlying skin diseases in the treatment area, photosensitivity, oral contraceptive pill use, hormone replacement therapy, and current pregnancy and breastfeeding. The patients who did not complete our treatment protocol or whose clinical photographs or records were missing were also excluded. Patients were first treated with QSNY (Medlite C6™, Hoya ConBio, Fremont, CA), with a 6-mm spot size, collimated homogeneous flat-top beam profile, and fluence of 2.1–2.5 J/cm² at 10 Hz. The clinical end point was slight erythema. Then, patients were immediately treated with LPNY (Cynergy multiplex™, Cynosure, MA) with a 7-mm spot size, 0.3 ms, and fluence of 15–17 J/cm² at 5 Hz. Ten treatment sessions were conducted at 1-week intervals, followed by maintenance treatment for approximately 10 months with the following treatment intervals: once every 2 weeks for the first 2 months, once a month for the next 3 months, and then 3 months later (Figure 1). On completion of the maintenance treatment, patients received follow-up treatment at 6-month intervals. All patients were instructed to use broad-spectrum sunscreen with a sun protection factor of 50 throughout the treatment period. Treatment response and adverse events were recorded at each visit. Digital photographs (Dermavision; OptoBioMed, Korea) were taken under the same conditions at each visit.

Two blinded dermatologists independently reviewed the clinical photographs to evaluate the treatment efficacy and adverse events. The severity and distribution of melasma were assessed using the photographs taken at baseline. Severity was scored using the modified Melasma Area and Severity Index (mMASI). Unlike the original MASI, mMASI does not consider homogeneity, and is calculated as follows: mMASI = 0.3 A(f) D(f) + 0.3 A(lm) D(lm) + 0.3 A(rm) D(rm) + 0.1 A(c) D(c), where A is the area of involvement (0–6 points: 0 = absent, 1 = <10%, 2 = 10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–89%, and 6 = 90–100%) and D is the pigment darkness (0–4 points: 0 = absent, 1 = slight, 2 = mild, 3 = marked, and 4 = severe). Two months after the 10-week treatment, the physician’s global assessment (PGA) and mMASI were scored. PGA was performed using a 5-point scale (0 = no improvement [0%], 1 = slight improvement [1–25%], 2 = fair [26–50%], 3 = good [51–75%], and 4 = excellent [76–100%]). Adverse events including mottled hypopigmentation and rebound hyperpigmentation were also recorded. Follow-up data recorded 2 months after completing the 10 treatment sessions were also reviewed, although not scored. Results were analyzed using the Wilcoxon signed-ranks test (SPSS 20.0, IBM, Armonk, NY), and a p value < 0.05 was considered statistically significant.

![Figure 1. Outline of the treatment schedule and evaluation.](image-url)
Results

A total of 30 Korean patients with Fitzpatrick skin type III–IV were included in this study. All patients were women, with a mean age of 37.8 (range, 27–56) years. The previous treatment that caused rebound hyperpigmentation included laser toning ($n=20$, 66.7%), IPL ($n=5$, 16.7%), fractional laser ($n=1$, 3.3%), chemical peeling ($n=1$, 3.3%), and combination treatment, which included laser toning plus chemical peeling ($n=2$, 6.7%) and laser toning plus fractional laser ($n=1$, 3.3%). The number of sessions in the 20 patients who received laser toning ranged from 5 to 25, with a median of 10. The number of sessions in the 5 patients who received IPL ranged from 1 to 10, with a median of 3. The duration since the onset of rebound hyperpigmentation ranged from 2 weeks to 2 years, with a median of 12 weeks. Twenty patients (66.7%) had localized melasma confined to the malar area, near the periorbital area, and 10 patients (33.3%) had a diffuse malar distribution. The baseline mMASI (mean ± standard deviation) was $10.48 \pm 3.64$, which significantly decreased to $3.22 \pm 1.45$ 2 months after completing the 10 treatment sessions ($p<0.001$). Twenty-four patients (80%) had PGA of grade 4 (76–100% improvement) and 6 patients (20%) had PGA of grade 3 (51–75% improvement) (Figures 2 and 3). None of the 30 patients showed any adverse events including more rebound hyperpigmentation or new formation of mottled hypopigmentation. All patients maintained the improved state in the long-term follow-up period of 1–3 years.

Discussion

Melasma is an acquired pigmentary disorder that is common in women with darker skin types, especially in East Asians. It is refractory to treatment with the conventional pigment-targeting laser treatment using the recommended fluence, which tends to result in rebound hyperpigmentation or aggravation of melasma. After retreatment with a higher fluence, the...
pigmentation may seem to improve in the short-term; however, the pigmentation worsens in the long-term, leading to a vicious cycle. Although the exact mechanism for the frequent occurrence of rebound hyperpigmentation during melasma treatment is not well understood, the complex pathophysiology of melasma may be involved. In addition to the increased pigmentation, the dermis shows more elastosis and vascularization than the perilesional skin in melasma (1,14,15). Recent studies on the pathogenesis of melasma reported an altered dermal environment and impaired basement membrane (1–3). When aggressive treatment such as high-fluence laser is administered, dermal inflammation could be induced via destruction of melanocytes, which in turn may influence the upregulation of stem cell factors and increase vascularity, thereby promoting melanogenesis (3). Furthermore, if the basement membrane is damaged, the melanin pigment and active melanocytes could fall or migrate into the dermal layer, allowing constant hyperpigmentation (1–3,13,14). Therefore, it is important to avoid aggressive melasma treatment that could induce dermal inflammation and basement membrane disruption.

Pulsed dye lasers (PDL) have been used to target vascularity and elastosis in the dermis of melasma patients (15). Furthermore, Passeron et al. conducted a prospective randomized split-face study comparing a triple combination cream with or without PDL in melasma patients. The results—immediately after treatment, as well as one summer later—demonstrated the beneficial effect of PDL. It was interesting to note that 3 years after the treatment, one of the participants presented with a relapse of melasma that completely spared the area previously treated with PDL. This strongly indicated that PDL has a preventive effect against relapses or aggravation of melasma through a decrease in the vascular component (15,16). In a similar way, at first, we administered PDL/LPNY treatment at 4-week intervals in combination with laser toning for treating rebound melasma and reduced the QSNY energy to levels lower than those used in conventional laser toning. The Cynergy multiplex™ used in this study is a combination device with a dual mode of 585-nm PDL and 1064-nm LPNY. Each of the 2 lasers can work in combination or separately. Although unsatisfactory, the results did not indicate aggravation.

We then attempted to combine low-fluence LPNY every week along with laser toning and also reduce the QSNY fluence. As shown in the results, 80% of the patients achieved 76–100% improvement and 20% achieved 51–75% improvement after 10 sessions of dual toning. None of 30 participants showed more rebound hyperpigmentation in the long-term follow-up period. With regard to mottled hypopigmentation, 12 patients (40%) had concomitant mottled hypopigmentation at the beginning of dual toning, lasting for a long time over the follow-up period, as they did not receive any treatment for hypopigmentation. Just as the pigmented regions lighten with dual toning, a reduction in contrast resulted in less remarkable hypopigmentation. Mottled hypopigmentation or punctuate leukoderma, another adverse event that can occur during melasma treatment, may be the result of a loss of function in the
melanocytes, possibly damaged from excessive laser energy (17–19). Although we did not perform statistical analysis, the mottled hypopigmentation resolved in approximately 50% of patients after 2 years and 80% after 3–4 years.

The quasi-long pulse or sub-millisecond pulse 1064-nm Nd:YAG laser used in this study has been termed the “genesis technique” and is used for nonablative skin rejuvenation. The wavelength of 1064 nm penetrates deep into the dermis and is mainly absorbed by water. With a long pulse duration and pulse stacking, it transfers the thermal energy to the surrounding deep dermal layer, which can stimulate collagen synthesis and dermal remodeling. Furthermore, it was revealed that the levels of the heat shock protein and transforming growth factor-beta were induced, whereas the levels of the proinflammatory cytokine interleukin-8 were reduced, which can contribute to dermal rejuvenation (11,20,21). Therefore, LPNY may contribute to stabilizing the melasma activity and preventing aggravation via dermal remodeling, although it does not directly destroy melanosomes.

Rebound hyperpigmentation or aggravation of melasma after treatment is a distinct phenomenon from postinflammatory hyperpigmentation or recurrence of melasma. Postinflammatory hyperpigmentation usually appears immediately after treatment, confined to the treatment field, without a time gap from treatment and then spontaneously fades away over a few weeks to months. Recurrence of melasma appears after a rather long time, for example, several months to years after cessation of treatment, and progresses slowly. Meanwhile, rebound hyperpigmentation tends to appear abruptly in an improved state in a few days to weeks after treatment. In the case of multiple sessions of laser toning, it tends to appear abruptly in an improved state after several sessions or in 2 months after completing multiple sessions. For this reason, we followed up patients 2 months after finishing the 10 treatment sessions. The pigmentation may darken rapidly, reaching levels more severe than the initial state. It can involve the originally normal, perilesional skin, which was suggested as dormant or subclinical melasma (13). As observed in our study, once the melasma is stimulated and activated to result in rebound hyperpigmentation, patients require a long time to recover without therapy. Although we cannot predict the occurrence of rebound hyperpigmentation, the suggested risk factors include the location of melasma on the periorbital thin skin or telangiectatic base, as well as use of excessive laser energy (22). Therefore, in such cases, more caution is needed.

**Conclusion**

A dual mode of low-fluence QSNY and LPNY, designated as dual toning, may represent a safe and effective retreatment for melasma aggravation after previous treatment. Rebound melasma is vulnerable to stimulation and deterioration, but may persist for a long time in the absence of therapy. Very-low-fluence QSNY may gradually lighten the pigmentation and LPNY may stabilize the activity of melasma to prevent further rebound via dermal remodeling. A prospective controlled split-face comparison study with histologic analysis is needed.

**Declaration of interest:** The authors report no declarations of interest. The authors alone are responsible for the content of the writing and paper.

**References**


