Efficacy of Combination Therapy for Melasma Using Low Fluence Q-Switched Nd:YAG Laser (LFQSNYL), Pulsed Dye Laser (PDL), High-Intensity Focused Ultrasound (HIFU), and Polynucleotides: A Case Report

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Abstract: Melasma is characterized by dark-brown patches on the face, and its treatment remains challenging due to its complex pathogenesis. This case report aims to evaluate the efficacy of a combination treatment using multiple targeted approaches, including 1064 nm Low Fluence Q-Switched Nd:YAG laser (LFQSNYL), 595 nm Pulsed Dye Laser (PDL), High-Intensity Focused Ultrasound (HIFU), and Polynucleotides (PN). A 41-year-old woman with Fitzpatrick skin type III and no known medical conditions presented to our clinic with pigmentation on both cheeks that had been present for seven years. Upon examination, she exhibited marked telangiectatic erythema within symmetric, reticulated hyperpigmented patches with irregular borders on both cheeks. Based on the clinical presentation, she was diagnosed with melasma. The patient received a total of five sessions of 1064 nm LFQSNYL combined with 595 nm PDL, two sessions of HIFU, and three sessions of PN treatment. The total treatment duration was four months, with intervals between each treatment modality ranging from one to three months. One month after the fifth treatment session, her modified Melasma Area and Severity Index (mMASI) score decreased from 13.2 to 3.3. The patient expressed high satisfaction with the overall outcome. In conclusion, the combination of LFQSNYL, PDL, HIFU, and PN may offer a promising approach to treating melasma, particularly in cases with telangiectasia. To fully establish the efficacy of this combination treatment, further clinical trials involving larger sample sizes, long-term follow-up, and optimization of treatment protocols are necessary.

Keywords: High intensity focused ultrasound, Low fluence Q-switched Nd:YAG laser, Melasma, Pulsed dye laser, Polynucleotides

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Introduction

Melasma is an acquired skin disorder that clinically presents as symmetrical hyperpigmentation, appearing as light brown to dark, muddy brown patches and macules on the face, typically affecting the forehead, cheeks, and chin. It is more commonly seen in individuals with darker skin tones, particularly those classified as Fitzpatrick skin types III and IV [1].

The main factors contributing to the development of this condition include ultraviolet (UV) radiation, female sex hormones, inflammation, and genetic susceptibility.

Treating melasma remains difficult due to inconsistent outcomes and frequent recurrences [2]. In managing this condition, it is important to approach melasma as both a pigmentation disorder and photoaging condition, and avoiding all known triggering factors. Available treatment options include topical depigmenting agents, oral tranexamic acid (TXA), and energy-based therapies. Energy-based devices improve melasma treatment by targeting melanin, addressing vascular components, and promoting skin rejuvenation [3].

Low Fluence Q-switched Nd:YAG laser (LFQSNYL) is the most widely used energy-based treatment for melasma, particularly among Asians. Studies have consistently shown that LFQSNYL whether used alone or combined with medications or other energy-based treatments, produces notable therapeutic effects [3]. This laser therapy is considered one of the most effective monotherapy for melasma, and when combined with other therapies, it tends to yield even better outcomes [4].

Pulsed dye laser (PDL) therapy is regarded as the gold standard for treating vascular lesions [5]. Increased vascularization in melasma has been identified through dermoscopy and reflectance confocal microscopy, with asignificant upregulation of vascular endothelial growth factor (VEGF) expression in melasma lesions [6]. Therefore, targeting vascular lesions in melasma with PDL may help suppress melanocyte activation. The addition of PDL therapy could be particularly beneficial for managing melasma that presents with a telangiectatic component [7]. By targeting blood vessels, PDL therapy reduces stimulation of melanocytes, thereby helping to prevent the recurrence of pigmentation spots [8].

High intensity focused ultrasound (HIFU) have also been investigated for the management of melasma. Theoretically, HIFU can stimulate neocollagenesis and enhance the photoaged condition of lesions, thereby contributing to the improvement of melasma [3]. The mechanism of HIFU involves the application of high-frequency ultrasound beneath the skin, causing targeted thermal damage at specific depths [9-11]. In a split-face study involving patients with melasma, the combination of HIFU and 2% hydroquinone showed significant improvement from baseline, although no significant difference was observed when compared to the side treated with 2% hydroquinone alone [11]. Choi et al. found that HIFU improved UVB-induced pigmentation in guinea pig skin, suggesting that it may have a mechanical destructive effect, removing pigment from the epidermis and upper dermis [9]. A study by Abdulhadi et al. showed that the combination of LFQSNYL and HIFU was more effective than using the laser alone in treating resistant melasma [12].

Polynucleotides (PN) are highly refined natural DNA fragments, consisting of deoxyribonucleotide chains ranging from 50 to 200 base pairs [13]. They exhibit anti-inflammatory, anti-ischemic, pro-angiogenic, and cell-stimulating properties [14]. Due to their ability to enhance tissue repair and regeneration, PN have been adopted for aesthetic purposes in facial and body rejuvenation [15]. In vitro studies found that PN reduces Microphthalmia-Associated Transcription Factor (MITF) signaling and downregulates melanogenic genes [16,17].

The histopathological features commonly seen in melasma include elevated melanin levels within keratinocytes and macrophages, an increased number of mast cells, dilated dermal vessels, solar elastosis, and disruption of the basement membrane [18]. Due to its complex pathogenesis, treatment strategies targeting various structural components of melasma have been suggested [19], including melanin production, vascularization, and basement membrane disruption. These approaches may

offer an effective treatment option. Therefore, this case report aims to evaluate the efficacy of a combination treatment with multiple targeted approaches, including LFQSNYL, PDL, HIFU, and PN, for melasma.

Case Presentation

A 41-year-old woman with Fitzpatrick skin type III and no known medical conditions, presented to our clinic with pigmentation on both cheeks that had been present for seven years. She reported that the pigmentation worsened after her second pregnancy. Her menstrual cycle is regular, and she is not using any hormonal contraception. There is no significant family history of pigmentation. She works as a finance manager in an indoor office and has minimal involvement in outdoor activities. She has no previous aesthetic history, such as chemical peeling or laser therapy. However, she has been using a topical depigmentation cream for the past year, with no observed improvement. Her skincare regimen includes toner, moisturizer, and sunscreen. On examination, there was marked telangiectatic erythema within symmetric, reticulated hyperpigmented patches with irregular borders on both cheeks **(Figure 1).** The clinical presentation led to a diagnosis of malar melasma.

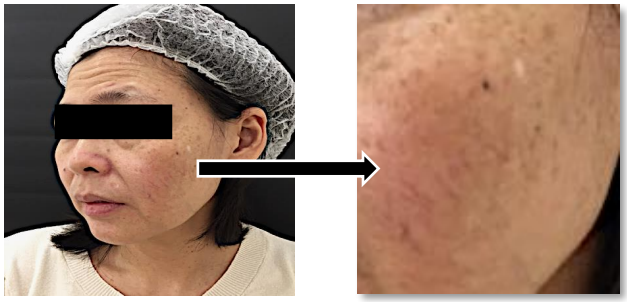

Figure 1 Pronounced telangiectatic erythema in a background of symmetric reticulated hyperpigmented patches with irregular borders.

Management and Outcome

The patient was treated with combination therapy consisting of LFQSNYL, PDL, HIFU, and PN for her melasma. Treatment was administered following written consent. The total duration of treatment was four months, with intervals for each treatment modality ranging from one to three months. The patient received a total of five sessions of 1064 nm LFQSNYL (Spectra XT™, Lutronic Corporation, Korea) with 595 nm PDL (Spectra XT™, Lutronic Corporation, Korea), two sessions of HIFU (Ultraformer III; Classys Inc., Seoul, Korea), and three sessions of PN (Plinest®, Mastelli, Sanremo, Italy) injections (Table 1).

Three-angle photographs were taken using a smartphone (iPhone model 7) at the initial session and at the final evaluation, one month after the fifth session. Improvement in melasma was assessed visually using the modified Melasma Area and Severity Index (mMASI) score. Patient satisfaction was also evaluated at the end of treatment. The patient indicated her satisfaction on a 5-point scale (very satisfied, satisfied, neither satisfied nor unsatisfied, unsatisfied, or very unsatisfied).

The fluence for the LFQSNYL laser was set at 0.90 J/cm², with a spot size of 8 mm and a pulse rate of 10 Hz, and 3 passes were performed on each side of the face. For the 595 nm PDL, the fluence was set at 0.3 J/cm², with a spot size of 5 mm and a pulse rate of 2 Hz, and one pass was performed on each side of the face. For PN, 2.0 mL was delivered subdermally to the face using a 27G, 38 mm cannula via the retrograde technique (0.1–0.2 cc per tract), primarily targeting areas affected by melasma. The HIFU device was used to target three different skin depths: 4.5 mm, 3.0 mm, and 2.0 mm. A total of 400 shots were delivered in each treatment session. For the 4.5 mm skin depth, the energy fluence was 0.6 J; for the 3.0 mm skin depth, the fluence was 0.3 J; and for the 2.0 mm skin depth, the fluence was 0.1 J. The patient underwent two sessions of HIFU,

with a three-month gap between sessions. After each treatment session, the patient was advised to apply sunscreen daily and maintain her regular skincare routine.

One month after the fifth treatment session, noticeable improvement in her melasma was observed. The patient's initial mMASI score of 13.2 was reduced to 3.3. Additionally, the redness associated with telangiectasia on her bilateral cheeks had diminished (Figure 3). The patient experienced mild discomfort in the mandibular region following the first HIFU session, which resolved within two days. No significant side effects, such as post-inflammatory hyperpigmentation (PIH) or scarring, were noted during the treatment period. The patient expressed being very satisfied with the overall outcome. A continuous follow-up was conducted three months after the final session, and no recurrence was observed. The patient's mMASI score remained at 3.3, and her telangiectatic erythema did not recur.

Table 1 Treatments administered in each session.

Session	QSNYL (1064 nm)	PDL (595 nm)	HIFU	PN-HPT
1	✓	✓		✓
2	✓	✓	✓	✓
3	✓	✓		✓
4	✓	✓		
5	✓	✓	✓	

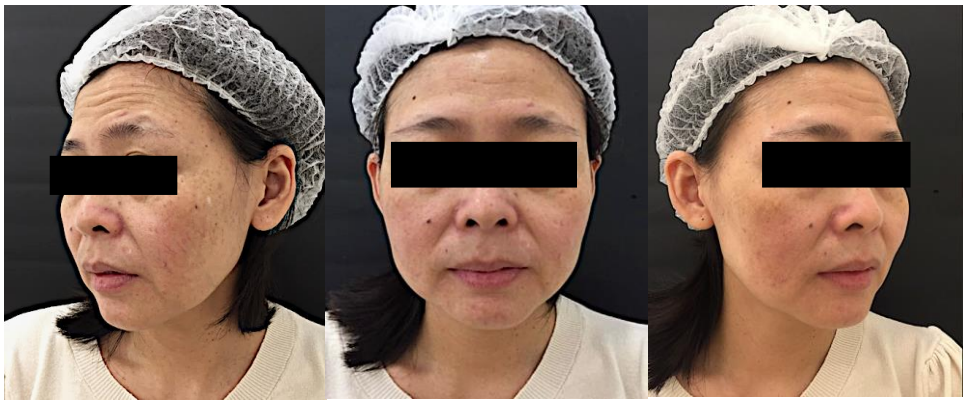

Figure 2. Clinical photograph of the patient showing left (45-degree), front, and right (45-degree) views at her first presentation. Pronounced telangiectatic erythema was noted against a background of symmetrical, reticulated hyperpigmented patches with irregular borders covering the bilateral cheeks.

Discussion

Managing melasma presents significant challenges due to the variability in treatment outcomes and frequent relapses, which can have a profound impact on patients' psychological well-being and overall quality of life. While energy-based therapies have shown promise in treating melasma, combination treatments targeting multiple factors may provide a more effective approach [3].

In this case report, we aimed to evaluate the effectiveness of combination therapy using a multi - targeted approach

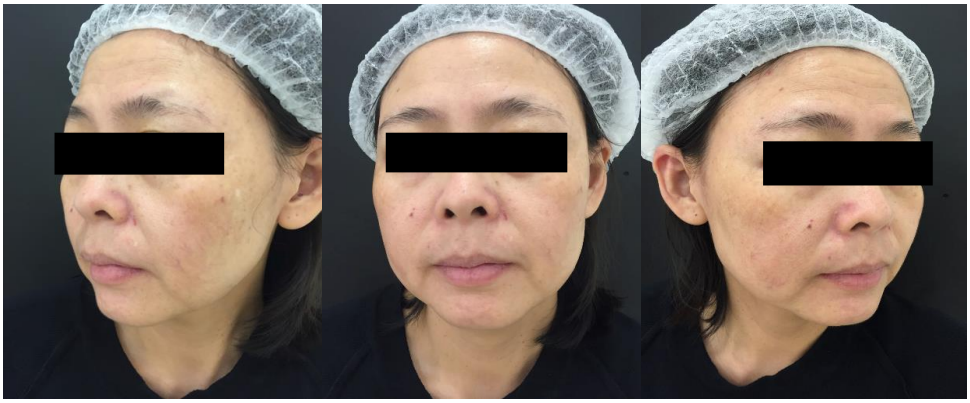

Figure 3. Clinical photograph of the patient showing left (45-degree), front, and right (45-degree) views one month after the fifth treatment session. The hyperpigmented patches have reduced, and telangiectatic erythema has improved.

involving LFQSNYL, PDL, HIFU, and PN for treating melasma. One month after completing five sessions of the combination treatment, the patient showed significant improvement, as evidenced by a reduction in her mMASI score. The observed improvement may be attributed to the various targeted mechanisms offered by the combination therapy administered to her.

LFQSNYL specifically target melanin by destroying intracellular melanosomes through subcellular selective photothermolysis [20]. It will preserve melanocytes, leading to a reduction in melanin at the affected site while minimizing both inflammation and side effects [3]. Additionally, according to Kim et al. targeting vascular components during melasma treatment is advantageous since increased vascularization is one of the histopathological characteristics of melasma, which may worsen the hyperinflammatory condition [21]. Therefore, the use of laser or light treatments that are absorbed by blood vessels, such as PDL, can reduce vascularization and improve the appearance of melasma [22]. PDL targets oxyhemoglobin in the blood vessels of the skin and is commonly used to treat various vascular conditions [7]. According to Kong et al., combining LFQSNYL with PDL may provide an effective therapeutic approach for melasma by addressing both melanin and vascular factors [7]. Furthermore, treatments that improve skin rejuvenation such as HIFU and PN are also beneficial, as melasma is recognized as a photoaging disorder characterized by solar elastosis and disruption of the basement membrane [23]. Therefore, the combination of LFQSNYL, PDL, HIFU, and PN in this study may be advantageous for the patient, as these therapies target different underlying factors.

Conclusion

The combination of LFQSNYL, PDL, HIFU, and PN may offer a promising approach for melasma treatment, particularly in cases with telangiectasia. This multifaceted approach targets different aspects of the condition, including pigmentation and vascular issues, which could lead to more effective and sustainable results. However, further studies are needed to validate these findings in a larger cohort, assess long-term outcomes, and determine the optimal treatment protocols.

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Potential Conflict of Interest

The author declares no potential conflicts of interest.

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