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Surgical Research

Safety and Efficacy of Combined Low Fluence Q-switched Nd:YAG 1064nm Laser with Pulsed Dye Laser 595nm in Melasma Control Among Malaysians: Does Adding Polynucleotides High Purification Technology (PN HPT™) Lead to a Difference?

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ABSTRACT

Background: *Melasma is a form of acquired skin hyperpigmentation that is more prevalent among middle-aged women with Fitzpatrick skin types III, IV, and V. While highly preventable, the condition has a relatively high recurrence rate, especially with monotherapy. As a result, evaluating the effectiveness of combination therapies may be beneficial in treating melasma.*

Methods: *This study retrospectively examined the medical records of 50 patients with melasma, divided into two groups. The first retrospective group of 25 patients had previously been treated with a low-fluence Q-switched Nd:YAG 1064nm laser and a pulsed dye laser 595nm, along with add-on intradermal Polynucleotides High Purification Technology (PN HPT™). The second group, also consisting of 25 patients, received treatment with a low fluence of a Q-switched Nd:YAG laser at 1064nm and a pulsed dye laser 595nm. The modified Melasma Area and Severity Index (mMASI) was compared retrospectively in the two groups over the observation period from November 2023 to June 2025.*

Results: *Both patient groups showed significant improvement by the end of the study compared to baseline, with a statistically significant difference between the two groups. The combination of laser and add-on PN HPT™ showed a more substantial reduction in mean mMASI scores than laser alone, both after 8 weeks (–12.8% vs. –9.3%, respectively) and 16 weeks (–24.4% vs. –16.0%, respectively, $p < 0.05$ between the two treatment groups).*

Conclusion: *Treatment with laser alone showed a slower improvement rate in the early weeks of the cycle compared to the combination of laser and add-on PN HPT™. Besides accelerating initial melasma improvement, the combination of subdermal PN HPT™ via cannula and laser led to a statistically significant and more noticeable improvement in hyperpigmentation disorders by the end of the cycle. However, more studies are needed to confirm the role of polynucleotides in melasma treatment.*

Keywords
Melasma, Q-switched Nd:YAG laser 1064nm, Polynucleotides High Purification Technology, PN HPT™, pulsed dye laser 595nm.

Introduction
The term melasma comes from the Greek word "melas," meaning black. Melasma, a benign skin condition, is an acquired form of skin hyperpigmentation characterized by irregular, blotchy, brownish areas with defined geographical borders. It has a higher prevalence among middle-aged women with Fitzpatrick skin phenotypes III, IV, and V [1]. The estimated prevalence in Southeast Asian populations reaches up to 40% in women and 20% in men [2]. Although it is largely preventable, treating this skin hyperpigmentation is challenging, with a relatively high tendency to recur [1,2]. The exact pathophysiology of melasma remains unknown, as the variable clinical presentations and histological characteristics observed in patients with this condition suggest multiple underlying mechanisms [1]. Wu et al. hypothesized that an imbalance between reactive oxygen species and antioxidant defense mechanisms contributes to the development of melasma [3]. Additionally, fluctuations in estrogen skin imbibition, impaired stratum corneum integrity, and UV ray exposure are other common co-determinants of melasma [4,5]. Finally, Kim et al. found a significantly increased density of the microvascular network in melasma skin, along with elevated levels of Vascular Endothelial Growth Factor (VEGF) [6].

Among the various melasma treatment options with different effectiveness and safety profiles studied so far, the currently recognized gold standard is tyrosinase-inhibiting topical hydroquinone. However, potential side effects, such as ochronosis and irritant dermatitis, warrant caution [7,8]. Azelaic acid, kojic acid, and arbutin are other alternative options with varying levels of effectiveness [9].

Research on non-ablative Q-switched Nd:YAG laser therapy for melasma has led to some success, but relapse remains a concern. A low-fluence Q-switched Nd:YAG laser 1064nm effectively targets melanin in melanophores with minimal damage to melanocyte integrity, making it a safe option for depigmentation. Furthermore, the pulsed dye laser 595nm is highly effective in decreasing vascular redness and inflammation. Despite these advances, melasma remains a chronic condition that tends to recur and requires ongoing management strategies [2,3,8].

Tranexamic acid (oral or topical) and natural-origin, highly purified, resorbable Polynucleotides High Purification Technology (PN HPT™) are other promising candidates that may have a role in managing melasma. Further data will help determine their efficacy and safety in this context [8,9]. For example, laser therapy combined with chemical peels and topical tranexamic acid, or triple combination creams, has shown superior results compared to laser therapy alone in treating melasma [10]. Dual toning with different laser technologies has also demonstrated significantly better outcomes [11,12]. Nevertheless, these novel strategies share drawbacks similar to those seen with traditional treatments. Individuals with Fitzpatrick skin types III through V present unique challenges due to the increased risk of post-inflammatory hyperpigmentation, a paradoxical darkening of the skin that can worsen melasma [8].

Regarding the rationale for the supportive role of PN HPT™ in managing melasma, PN HPT™-based hydrogels possess scavenger activity against reactive oxygen species, a property that is potentially useful for the protection of skin microenvironment from oxidative stress, the promotion of cell vitality, and extracellular matrix deposition [13].

Based on this evidence, this study aims to retrospectively compare the effectiveness and safety of combining a low-fluence Q-switched Nd:YAG laser 1064nm, pulsed dye laser 595nm, and Polynucleotides High Purification Technology (PN HPT™) with the same laser protocol without the PN HPT™ add-on for treating melasma.

Materials and Methods
Retrospective Design and Sample Size Estimation
The retrospective review of medical records related to the treatment of melasma at UR KLINIK in Malaysia spanned a period of twenty months, from November 2023 to June 2025. A sample size of 25 patients per group, estimated using the G-Power sample size calculator software version 3.1.9.7 with an effect size of 0.06, would achieve a discriminating power of 0.95 (the probability of avoiding the ß-risk of a false positive outcome) at a significance level of 0.05 (the probability of incurring a false negative).

Retrospective eligibility criteria
Inclusion criteria: Malaysian citizens aged 35 to 65 years, regardless of gender or ethnic background (Malay, Chinese, or Indian), with Fitzpatrick skin phototype III or IV, diagnosed with melasma, and scored using the modified Melasma Area and Severity Index (mMASI). Eligible patients were those who had completed three sessions of a combined low-fluence Q-switched Nd:YAG laser 1064nm and pulsed dye laser 595nm at four-week intervals, either alone or with the addition of intradermal PN HPT™ during the same session.

Individuals with known underlying medical conditions, pregnant women, and subjects receiving oral isotretinoin treatment or adjunctive therapies such as High-Intensity Focused Ultrasound, oral tranexamic acid, fillers, or topical treatments were not eligible for enrollment. Additionally, individuals with incomplete consent forms and medical records, including missing demographic data, photographs, and treatment parameters, were also excluded.

Retrospective treatment groups
After the preliminary screening, all eligible patients were divided into two groups:

- Retrospective Group 1: Patients who previously received energy-based treatment (low-fluence Q-switched Nd:YAG

laser 1064nm and pulsed dye laser 595nm) with add-on PN HPT™ treatment, performed during the same three sessions at four-week intervals.

- Retrospective Group 2: Patients who previously received only energy-based treatment at four-week intervals.
- The five-angle photographs from week 1 (baseline), week 8, and week 16, along with adverse effects such as erythema, swelling, burns, or blistering during treatment, were extracted from the clinical archived records for both groups.

Procedural details

Q-switched Nd:YAG 1064nm laser calibration: specific fluence of 0.5 to 1.0 J/cm^2, spot size of 8 mm, and frequency of 10 Hz; pulsed dye 595nm laser calibration: fluence of 0.15 to 0.30 J/cm^2, spot size of 5 mm, frequency of 2 Hz. The manufacturer of both devices is Lutronic Corporation, Goyang-si, Republic of Korea.

Add-on PN HPT™ treatment at all three sessions (retrospective Group 1): sterile, viscoelastic, phosphate-buffered gel containing 20 mg/mL of PN HPT™ in 2-mL single-use, apyrogenic prefilled syringes (CE-marked Class III medical device Plinest®, Mastelli Srl, Sanremo, Italy). PN HPT™ dose and administration: 2.0 mL (one Plinest® syringe) via a 27G 38 mm cannula for subdermal delivery using the retrograde method (0.1- 0.2 cc each tract) over the facial melasma area. No post-treatment medication was administered, and patients were instructed not to massage the treated areas.

Assessments

The retrospective assessment of melasma severity was carried out using the modified Melasma Area and Severity Index (mMASI)[17] (Figure 1) based on two parameters: the pigmentation's darkness and the extension of the affected area. The darkness of the pigment was visually rated on a scale from 0 (no pigmentation) to 4 (severe pigmentation). In addition to the initial baseline mMASI evaluation at the first treatment session, the authors conducted two additional follow-up mMASI assessments at 8 and 16 weeks after the baseline.

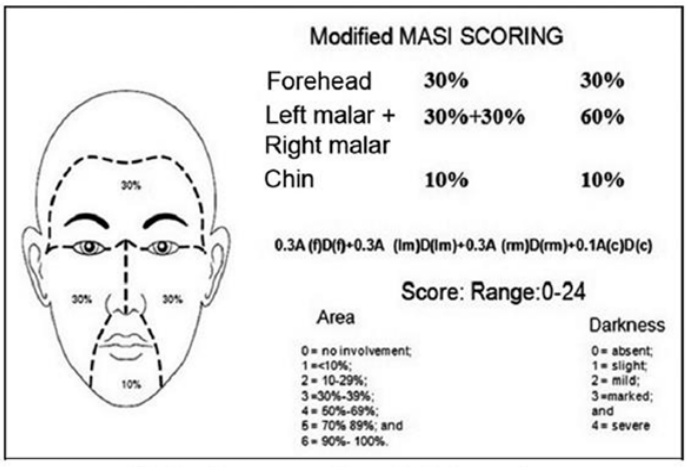

Figure 1: Modified Melasma Area and Severity Index (mMASI) score. Reproduced from Nicole Ng I et al., under the terms of a Creative Commons CC BY-NC 4.0 License [17].

The authors divided the face affected by melasma into four areas: the forehead, left malar region, right malar region, and chin. The pigmentation in each area was measured on a scale from 0 (no pigmentation) to 6 (pigmentation covering 90-100% of the area). Multiplying the scores for the size of the facial area and pigment darkness for each facial region gave the region's total score. The total mMASI score was calculated by adding the scores for all four facial areas computed using the formula 0.3A (forehead) x D(forehead) + 0.3A(left malar) x D(left malar) + 0.3A(right malar) x D(right malar) + 0.1A(chin) x D (chin) where A is the area surface and D is darkness. The total mMASI score can range from 0 to a maximum of 24, with a higher score indicating more severe melasma.

Two groups of well-trained independent third-party evaluators holding a Letter of Credentialing and Privileging (LCP) in aesthetics, according to local certification regulations, assessed the iconographic evidence using the five-angle photograph technique (Figure 2) and scored it. Figure 3 shows an example of the five-angle photograph technique. The evaluators had no relationship with the investigators or affiliated institutions to ensure an unbiased assessment of the data. All adverse reactions occurring throughout the treatment cycle were recorded and analyzed.

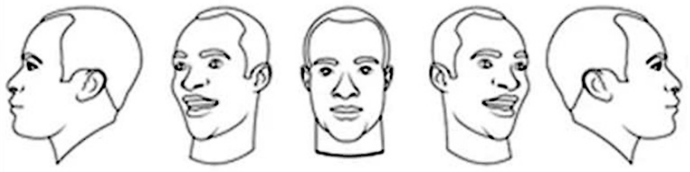

Figure 2: The five-angle-photograph assessment technique. Reproduced from Nicole Ng I et al., under the terms of a Creative Commons CC BY-NC 4.0 License [17].

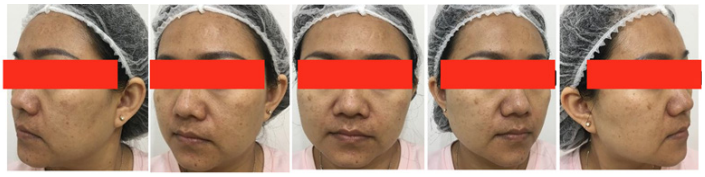

Figure 3: Shows an example of the five-angle photograph assessment technique: a sequence of photos taken at baseline in a Fitzpatrick type IV woman. Reproduced and adapted from Nicole Ng I et al., under the terms of a Creative Commons CC BY-NC 4.0 License [17].

Statistics

The Statistical Package for the Social Sciences (SPSS) version 23.0 was used for inferential statistical tests. The non-parametric Kruskal-Wallis test for independent samples (non-parametric independent-measure ANOVA) was employed to determine if there was a significant divergence from the null hypothesis (no divergence) in the curves for the mean Group 1 and Group 2

mMASI scores. If a significant difference was found, the authors used the non-parametric Šidák test for multiple comparisons to assess whether there were significant differences between the two groups at weeks 8 and 16. The authors also used the Friedman test (non-parametric repeated-measures ANOVA) to evaluate differences across different time points (week 8 vs. baseline, week 16 vs. baseline, and week 8 vs. week 16) within each Group 1 and Group 2 cohort. Significance was set at a p-value of less than 0.05 for all statistical inferences.

Safety Assessments

Before the laser treatment, the investigators conducted a safety test on the patients' hands to evaluate their comfort level and adjust the laser device settings to maximize tolerance and effectiveness. They also recorded all adverse reactions observed during treatment, including those typical of laser use, such as redness, swelling, burns, or blisters.

Ethics

The Medical Research Ethics Committee of the UMRA Hospital (UMRAMREC) approved the study. Data were anonymized to protect confidentiality.

Results

Table 1: Demographics of the retrospectively enrolled patients and distribution of the hyperpigmentation diagnoses between the two groups. ABNOM: Acquired Bilateral Nevus of Ota-like Macules; SD: standard deviation.

	Group 1 — add-on PN HPT™ (n = 25)	Group 2 — no add-on PN HPT™ (n = 25)
Women/men ratio	25/0	24/1
Age group (years)	**n (%)**	**n (%)**
31-40	0 (0%)	2 (8%)
41-50	11 (44%)	11 (44%)
51-60	11 (44%)	10 (40%)
61-70	3 (12%)	2 (8%)
Mean age ± SD (median)	51.7 ± 7.31 (51)	50.6 ± 6.73 (50)
And less		
Type III	14 (56%)	22 (88%)
Type IV *	11 (44%)	3 (12%)
Diagnosis		
Melasma only *	17 (68%)	4 (16%)
Melasma coexisting with other hyperpigmentation disorders (e.g., solar keratosis, freckles, ABNOM)*	8 (32%)	21 (84%)

* Proportions significantly unbalanced (chi-square assessment).

Table 1 illustrates the demographics of 50 patients retrospectively enrolled from the total pool of melasma patients treated at the investigators' clinical facilities during the specified period. These patients were evenly divided into two groups: Group 1 (combined laser treatments with add-on PN HPT™) and Group 2 (combined laser treatments without add-on PN HPT™). The average age at baseline was similar between the two groups; however, the distribution of Fitzpatrick skin types varied significantly, with a higher percentage of Fitzpatrick type III and a lower percentage of type IV in Group 2 compared to Group 1. The diagnoses also revealed slight differences, with Group 2 having significantly more cases of pigmentation disorders different from pure melasma.

Table 2 compares the effectiveness of the two treatment strategies, combined laser and PN HPT™ versus laser-only, over the 16-week retrospective observation period in terms of the mMASI score. At baseline, the Group 1 add-on group had a higher baseline mMASI score than the Group 2 no-add-on group (+14.7%), indicating slightly more severe pigmentation disorders in the add-on group. At the first follow-up assessment, 8 weeks after baseline, both groups showed improvements in the mMASI score compared to baseline; however, the reduction was tendentially more substantial in the add-on PN HPT™ group compared to the no-add-on PN HPT™ group (Group 1, –12.8%; Group 2, –9.3%; $p < 0.05$ vs. baseline for both groups, no significant difference between the two groups after 8 weeks).

By the last follow-up visit, 16 weeks after the initial visit, the mMASI score showed a significant additional decrease in treatment Group 1 (add-on PN HPT™) compared to the intermediate visit (–13.3%, $p < 0.05$). In contrast, treatment Group 2 (no-add-on PN HPT™) exhibited only a non-significant trend toward further decrease compared to the intermediate visit (–7.3%). Overall, at the end of the retrospective follow-up, the difference in mMASI score reduction between Group 1 (add-on) and Group 2 (no-add-on), compared to baseline, was highly significant (–24.4% vs. –16.0%; $p < 0.01$).

Table 2: Comparative efficacy of laser therapy with add-on PN HPT™ versus laser therapy without add-on PN HPT™ on melasma hyperpigmentation in Malaysian patients: mean mMASI scores and medians (within parentheses) over the 16-week total retrospective observation period.

Mean mMASI scores at the three assessment times			
Treatment Type	**Baseline**	**8th week**	**16th week**
Group 1 — add-on PN HPT™	8.6 ± 4.20 (8.6)	7.5 ± 3.99* (6.8)	6.5*# ± 2.59 (6.5)
Group 2 — no add-on PN HPT™	7.5 ± 2.14 (8.0)	6.8 ± 1.92 (6.5)	6.3 ± 1.88 (6.7)

* $p < 0.05$ vs. baseline; # $p < 0.01$ vs. add-on PN HPT™ group.

Demonstrative photographs taken by the authors at baseline, week 8, and week 16 in three patients in the add-on PN HPT™ treatment group (patients 1, 4, 13) and in the control group treated only with the standard double-laser strategy (patients 37, 43, 50) are available in the Supplementary files section.

Discussion

In Malaysia, melasma is a common skin hyperpigmentation disorder that mainly affects individuals with Fitzpatrick skin

types III and IV. However, its multifactorial pathology remains challenging, involving interactions among mast cells, keratinocytes, neovascularization, and basement membrane disruption [14-16].

In treating hyperpigmentation, the low-fluence Q-switched Nd:YAG laser 1064nm and the pulsed dye laser 595nm complement each other. Penetrating deeply into the skin, the low-fluence Q-switched Nd:YAG 1064nm laser is especially effective at targeting and breaking down melanin in the dermis, while minimizing the risks of thermal damage. The immune system then clears away the broken-down melanin particles [1,17]. Additionally, the low-fluence Q-switched Nd:YAG laser 1064nm lowers the risk of post-inflammatory hyperpigmentation, making it suitable for darker skin as well [11].

Conversely, the pulsed dye laser 595nm is mainly absorbed by hemoglobin, although it also provides a beneficial secondary effect on melanin. It is primarily effective for treating vascular lesions. Still, it can also improve skin tone by reducing redness and enhancing overall skin complexion by targeting the vascular component associated with pigmented lesions without causing significant damage to surrounding tissues. When treating melasma and other forms of hyperpigmentation, the pulsed dye laser 595nm is especially useful when combined with other treatments, such as the low-fluence Q-switched Nd:YAG laser at 1064nm [16].

The study confirmed that the double-laser treatment led to a notable reduction in total mean mMASI scores over 16 weeks compared to baseline, with significant improvement seen as early as the eighth week, and high safety. An add-on PN HPT™ treatment contributed to achieving a faster and more significant improvement in mean mMASI scores by the end of the 16-week follow-up period.

PN HPT™ are DNA fragments extracted from the gonads of salmon trout (*Oncorhynchus mykiss*) through an original high-purification technology (HPT™). This technology, developed by Mastelli Srl, provides high-quality DNA while minimizing immunological side effects. Thanks to their hydrophilic polyanionic structure, PN HPT™ bind water molecules in aqueous solutions and become a hydrogel, providing a biocompatible scaffold for cells [13,19,20]. PN HPT™ hydrates the dermal microenvironment, providing a short-term tissue-filling effect. In the long term, the PN HPT™ ingredient of the Plinest® medical device physiologically activates dermal fibroblasts by passively replenishing the tissue pools of nitrogen bases and nucleotide precursors [19-21]. After injection, thanks to their biocompatibility and moisturizing and viscoelastic properties, PN HPT™-based hydrogels fill gaps within tissues, providing immediate and temporary viscoelastic support by restoring tissue lift, turgor, and volume. The enhanced skin hydration, turgor, and firmness improve skin texture, support the regenerative capacity of skin cells, extracellular matrix deposition and organization, and contribute to a more youthful appearance [19-23].

Currently, speculating on how PN HPT™ cooperate with laser treatment in improving the skin appearance in melasma and hyperpigmentation disorders is not straightforward. In line with Kim's hypothesis on the etiology of melasma, supporting the fibroblast vitality and thereby the dermal microenvironment will indirectly fine-tune the deranged microvascular network in the dermis [6]. Moreover, PN HPT™ hydrogels act as scavengers of reactive oxygen species [13,19], thus correcting the imbalance with physiological antioxidant defense mechanisms hypothesized by Wu et al. [3]. Summarizing, the benefits of combining the gold-standard laser treatments of melasma and hyperpigmentation skin disorders with add-on PN HPT™ appear undeniable, but how this cooperation operates remains an open question.

Study limitations

This study has several limitations that should be taken into consideration. Statistical analysis focused solely on improvements in mMASI scores without evaluating other important skin parameters such as overall skin quality, hydration, or pore size. Additionally, the retrospective study design may introduce selection and recall biases, which can impact the validity of the results. Future research should include prospective controlled studies with a broader assessment of skin health to provide a more complete understanding of treatment outcomes.

Conclusions

The combination of three sessions of low-fluence Q-switched Nd:YAG laser 1064nm, pulsed dye laser 595nm, and subdermal PN HPT™ via cannula (Plinest®) led to a faster and more significant reduction in mMASI scores with no notable side effects compared to the double laser treatment without add-on PN HPT™. Future research on melasma and hyperpigmentation disorders should explore more thoroughly the impact of PN HPT™ on skin quality and hydration. Additionally, future clinical studies should consider extending their duration and paying closer attention to the recurrence rate of melasma.

Acknowledgments

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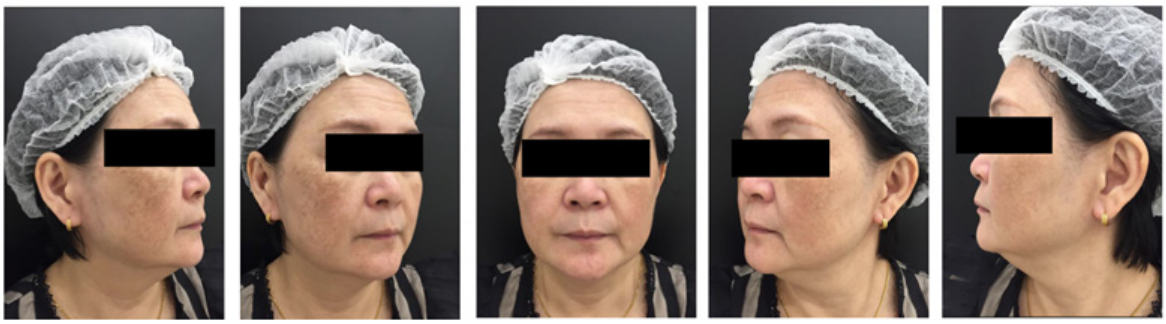
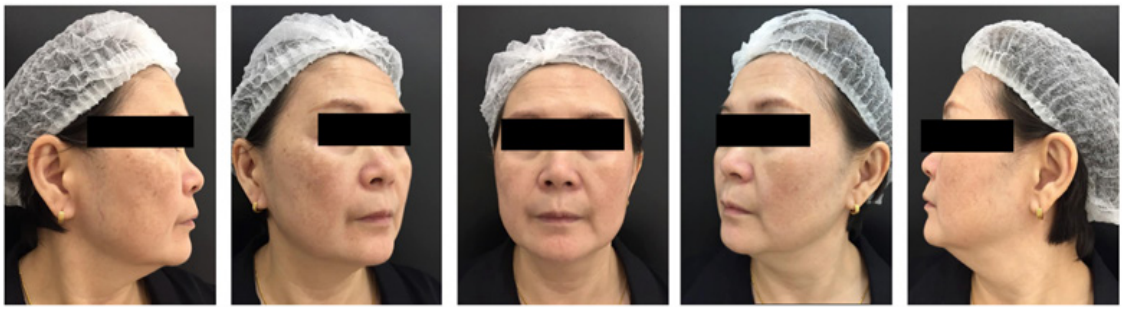
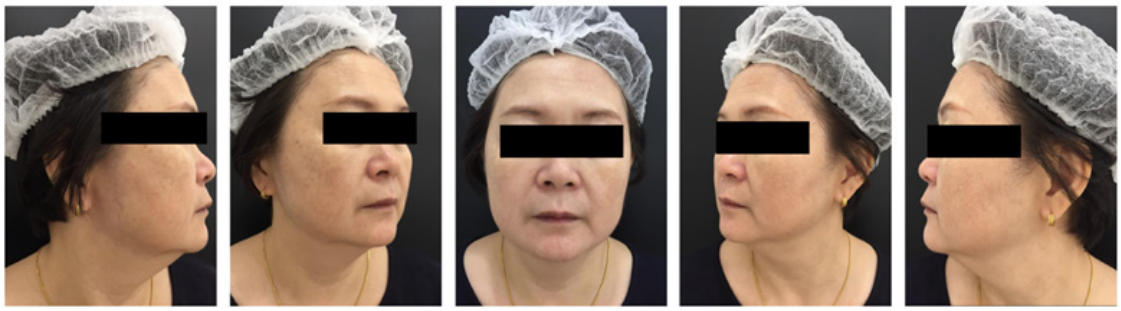
Supplementary
Add-on PN HPT™



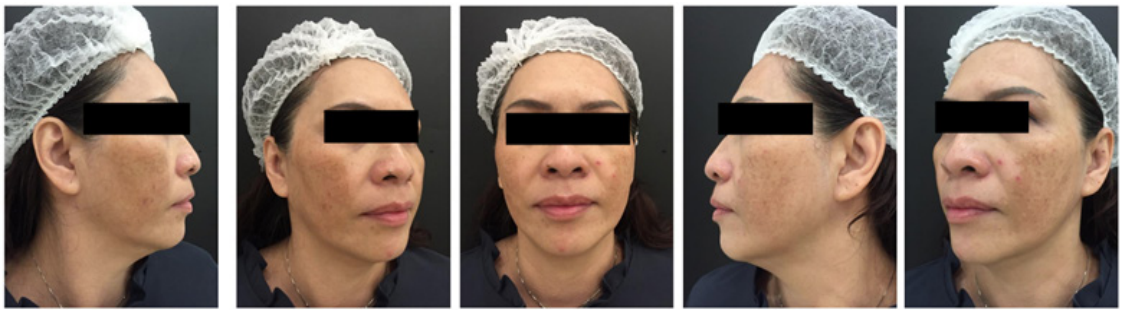
Add-on PN HPT™ — Patient 1, baseline



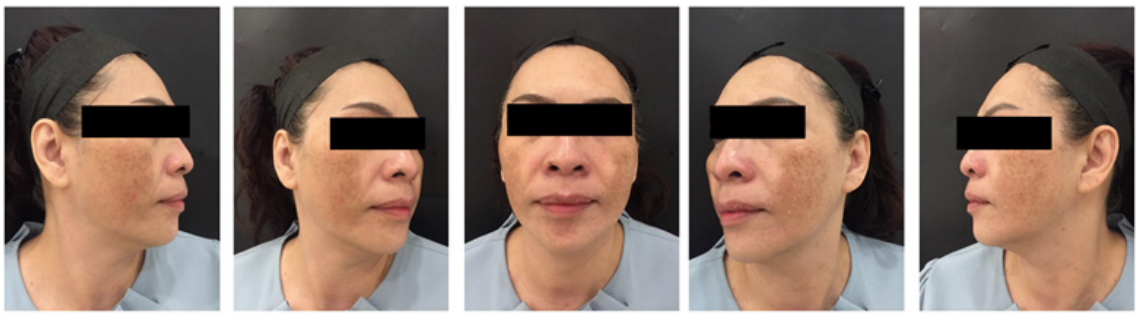
Add-on PN HPT™ — Patient 1, week 8



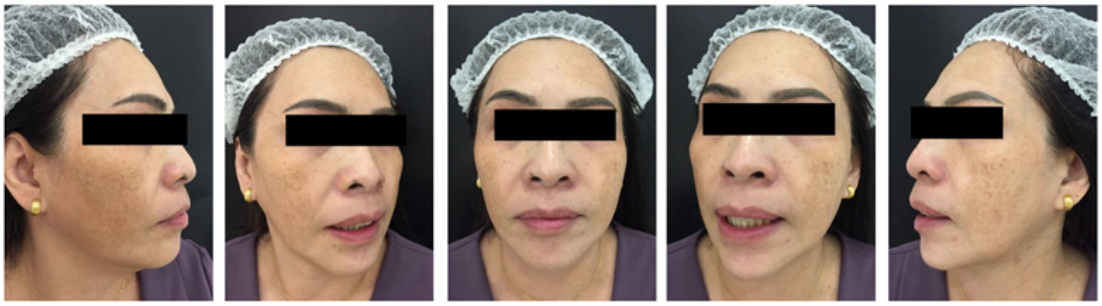
Add-on PN HPT™ — Patient 1, week 16



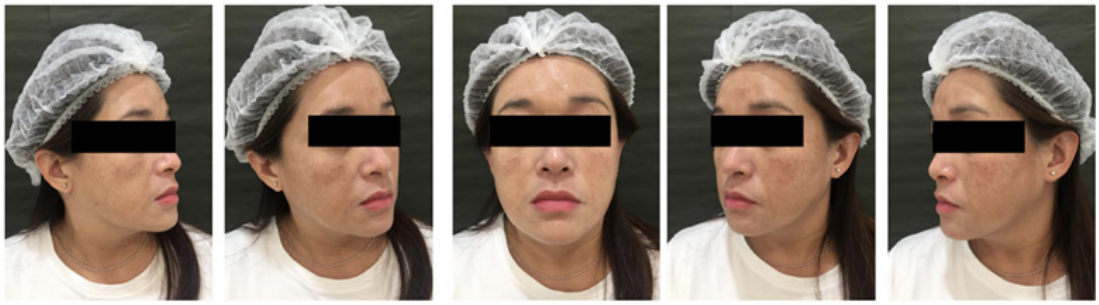
Add-on PN HPT™ — Patient 4, baseline



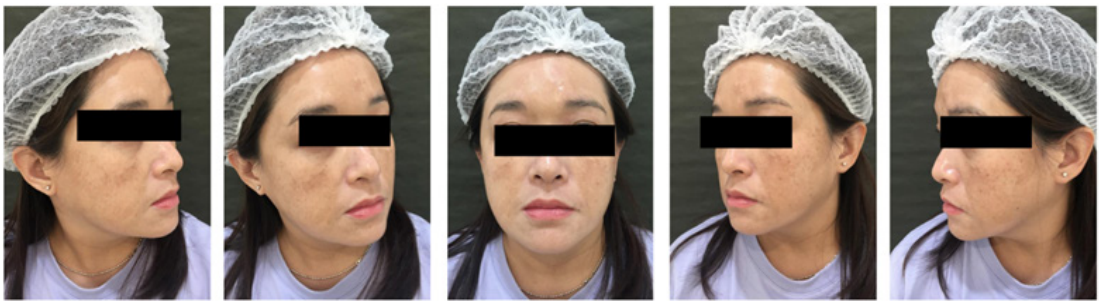
Add-on PN HPT™ — Patient 4, week 8



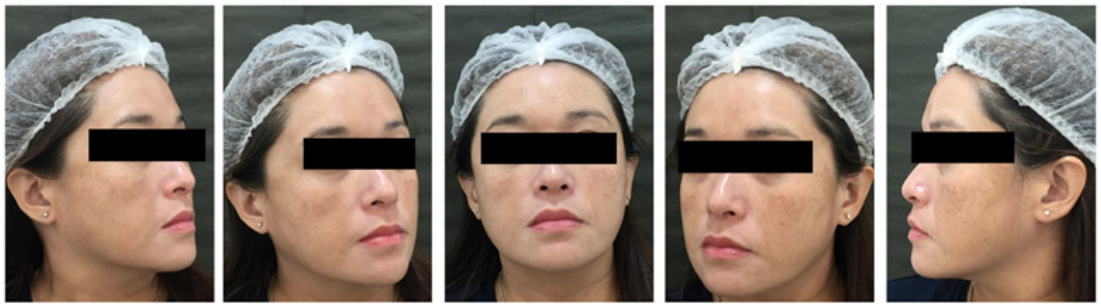
Add-on PN HPT™ — Patient 4, week 16



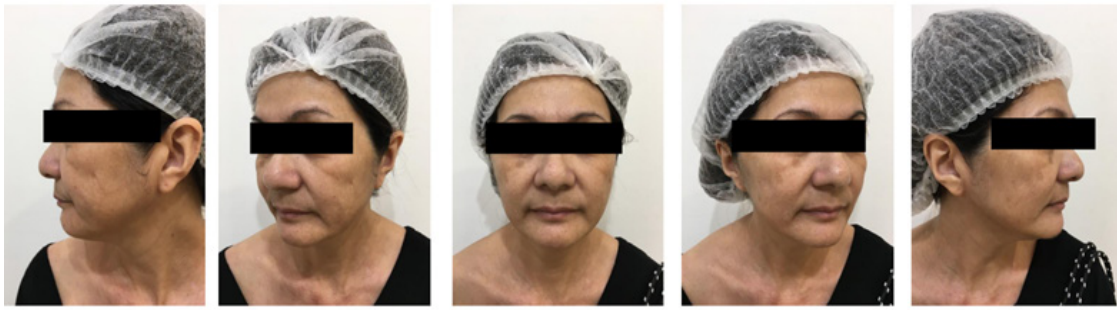
Add-on PN HPT™ — Patient 13, baseline



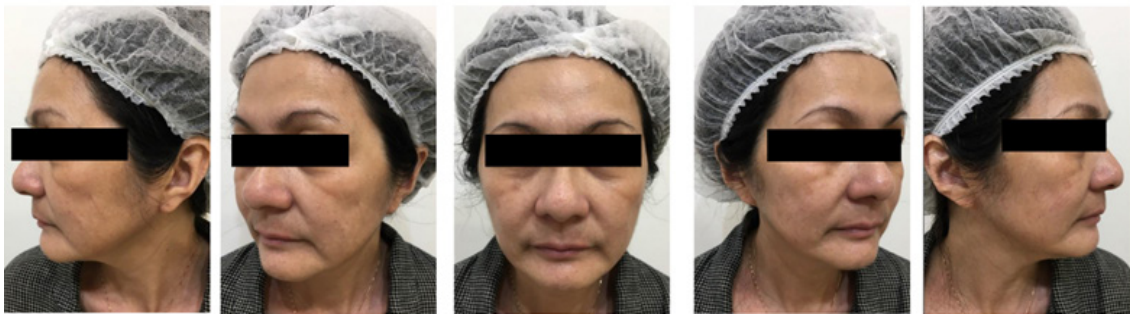
Add-on PN HPT™ — Patient 13, week 8



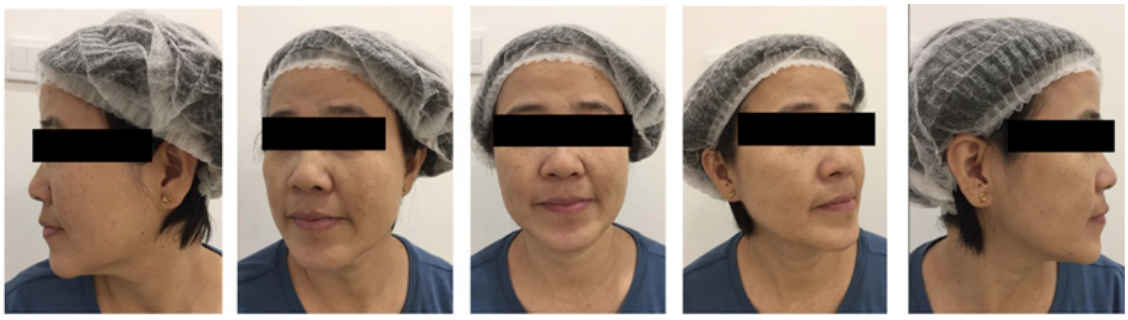
Add-on PN HPT™ — Patient 13, week 126



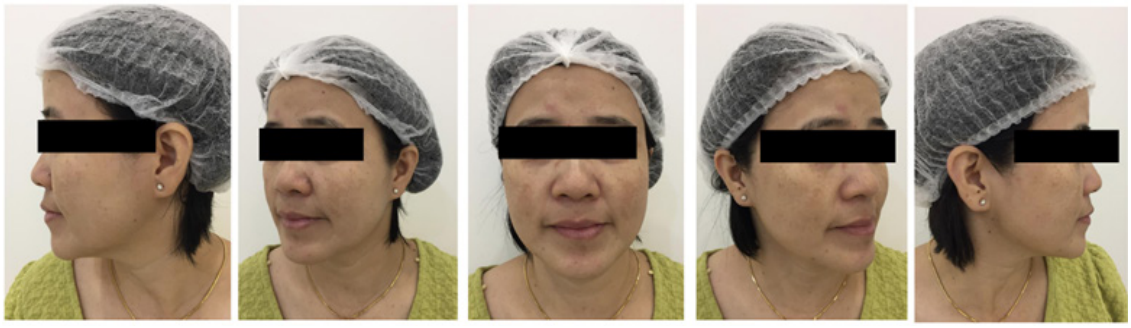
Only laser treatment — Patient 37, week 8



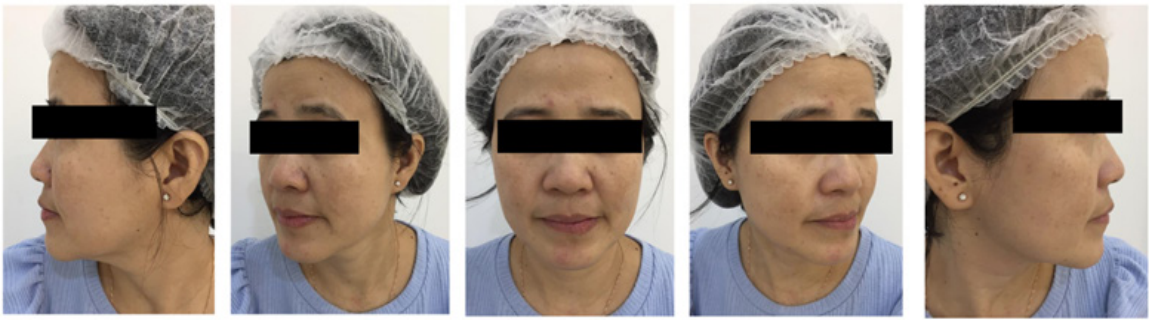
Only laser treatment — Patient 37, week 16



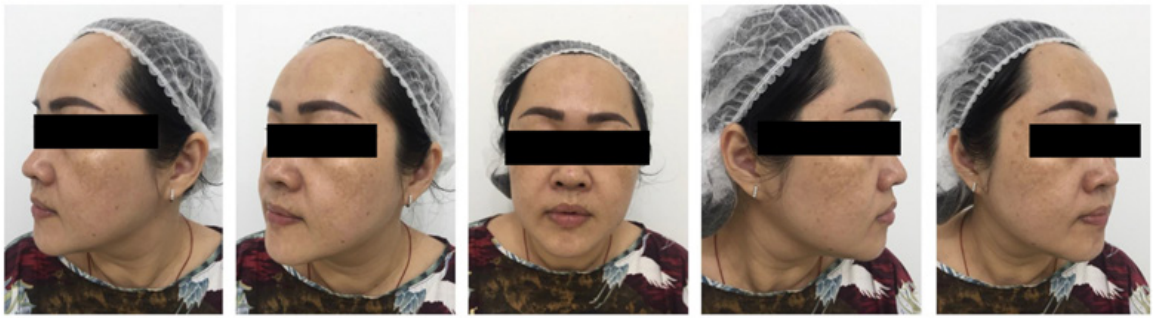
Only laser treatment — Patient 43, baseline



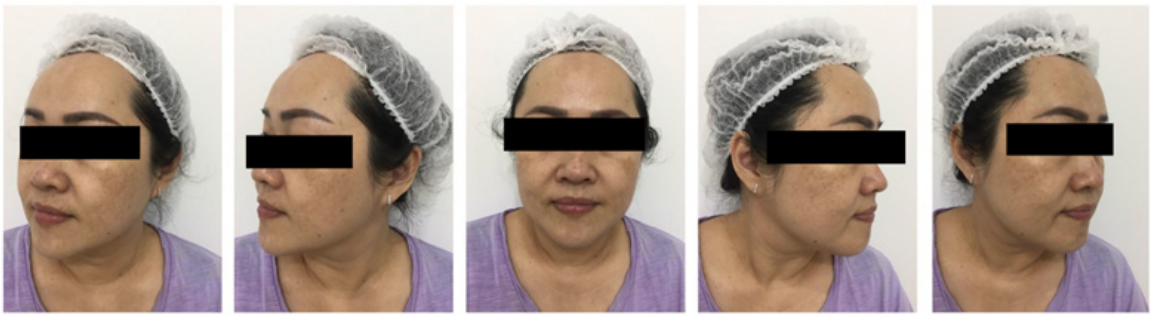
Only laser treatment — Patient 43, week 8



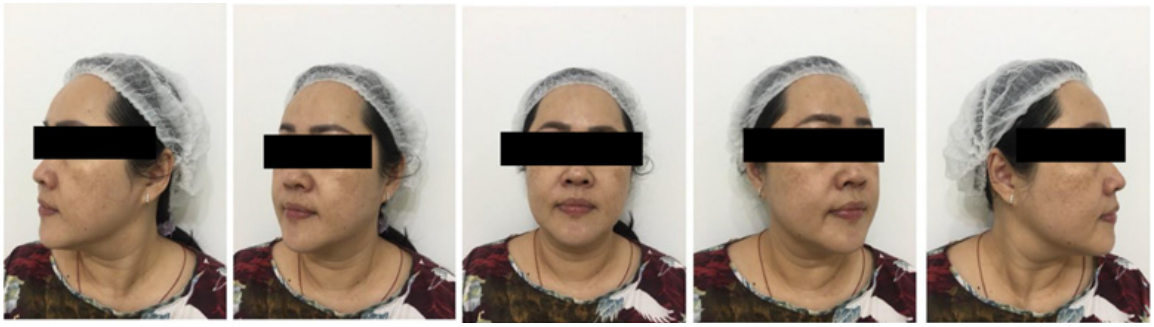
Only laser treatment — Patient 43, week 16



Only laser treatment — Patient 50, baseline



Only laser treatment — Patient 50, week 8



Only laser treatment — Patient 50, week 16