A COMPARATIVE STUDY ON THE EFFICACY OF FRACTIONAL Q-SWITCHED Nd:YAG LASER VERSUS LOW-FLUENCE Q-SWITCHED Nd:YAG LASER FOR FACIAL MELASMA IN THAI FEMALES

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IN
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SCHOOL OF ANTI-AGING AND REGERERATIVE MEDICINE
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THESIS COMMITTEE

.....CHAIRPERSON
(Prof. Dr. Thamthiwat Nararatwanchai)

.....ADVISOR
(Assist. Prof. Dr. Sunisa Thaichinda)

.....EXTERNAL EXAMINER
(Assoc. Prof. Dr. Wisuit Pradidarcheep)

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Nuttha Meesuntorn

Thesis Title	A Comparative Study on the Efficacy of Fractional Q-switched Nd:YAG Laser Versus Low-Fluence Q-Switched Nd:YAG Laser for Facial Melasma in Thai Females
Author	Nuttha Meesuntorn
Degree	Master of Science (Dermatology)
Advisor	Assist. Prof. Sunisa Thaichinda

ABSTRACT

Background: Low-fluence 1064 nm Q-switched Nd:YAG laser has recently been shown to be effective for the melasma treatment.

Objective: The purpose of this study was to compare collimator mode to fractional mode to evaluate the clinical efficacy and safety of low-fluence 1064 nm Q-switched Nd:YAG laser treatment of melasma in Thai females.

Methods: Eighteen patients with melasma underwent 16 weeks of twice a month treatments, using a Q-switched Nd:YAG laser (Helios II by LASEROPTEK) with parameters set for 750 mJ, piece 8 mm (1.95 J/cm^2), repetition rate 10 Hz, 2 passes for collimator mode and 850 mJ with fractional handpiece (3.4 J/cm^2) repetition rate 3 Hz, minimal overlapping, 2 passes for fractional mode. Patients and investigators evaluated the intensity of pigmentation by using MASI score and melanin index every 4 weeks and followed up at 4 weeks after complete 6 sessions of treatments. The objective assessment was also performed with VISIA and Mexameter tool.

Results: The result also revealed that there was constantly decreased MASI scores and melanin index after each treatment interval for all age groups during the course of 12 weeks treatment. Treatment was most effective on week 12 for all age groups. MASI scores and melanin index are rebounded after treatment termination on week 16, but still considerably lower than the mean MASI score and mean melanin index before recorded treatment at baseline. None of the 18 patients showed any signs of severe side effects during the course of the treatment.

Conclusion: Collimator and fractionl mode of low-fluence 1064 nm Q-switched Nd:YAG laser had no difference on the efficacy and both are effective to treat melasma without serious side effects.

Keywords: Low-Fluence 1064 nm Q-switched Nd:YAG Laser/Melasma/Collimator Mode/ Fractional Mode

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CHAPTER 1

INTRODUCTION

1.1 Background

Melasma is a disorder of acquired focal symmetric facial hyperpigmentation. The disorder is chronic, and its etiological basis is not known. Estrogen and sun exposure have been postulated to have central roles due to the association of melasma with pregnancy or use of oral contraceptives and its exacerbation with sun exposure. Risk factors include darker Fitzpatrick skin types (especially III and IV), family history, ultraviolet exposure, and thyroid disease (Kauh & Zachian, 1999). Although melasma itself does not represent a strictly therapeutic indication, it poses a substantial emotional and psychological burden on patients and adversely affects the patient's quality of life. Patients often present themselves to dermatologists to seek cosmetic treatment (Pawaskar et al., 2007).

The most commonly advised treatment begins with meticulous sun avoidance and use of sun protection products, which approach on its own yields improvement. Additional therapies have relied on bleaching agents, primarily hydroquinone of topical therapies, hydroquinone had been considered the gold standard, but recent safety concerns, including the risk of exogenous ochronosis or more serious effects due to its cytotoxic effects (Draelos, 2007). Lasers could be expected to produce more durable effects, by virtue of their longer-term changes on skin structure and function.

The 1,064-nm Q-switched neodymium-doped yttrium aluminum garnet (QS Nd:YAG) laser is widely used in cosmetic laser dermatology for pigmented and vascular lesions and removal of tattoos and unwanted hair. Over the last few years, the 1,064-nm QS Nd:YAG laser has increasingly been used for nonablative skin

rejuvenation and melasma in Asian countries. In “laser toning”, multiple passes of a low-fluence laser (1.6–3.5 J/cm^2) are delivered through a large spot size (6–8 mm) to optimize energy delivery and achieve mild erythema as the clinical end-point. The intention is to have multiple laser treatments at subthreshold fluence to obtain clinical effects with less down time (Jeong, Shin, Yeo, Kim, & Kim, 2010). Sub-thermolytic (sometimes referred to also as sub-ablative) Q-Switched Nd:YAG laser therapy is becoming common for skin rejuvenation and the treatment of various skin imperfections, among them Melasma. This treatment modality has proven to be especially popular in the Asian world.

Although the exact mechanism which low-fluence 1,064-nm QS Nd:YAG laser improves melasma is unclear. It has been proposed that, by delivering repetitive laser energy using a sub-photothermolytic fluence (<5 J/cm^2) over a large spot size, melanin granules are fragmented and dispersed into the cytoplasm without cellular destruction. The term “subcellular selective photothermolysis” has been proposed to describe the mechanism for improvement of melasma with low-fluence 1,064-nm QS Nd:YAG laser (Mun, Jeong, Kim, Han, & Kim, 2011).

Fractional photothermolysis (FP) has been recently introduced as a new concept in dermatologic laser medicine. Fractional photothermolysis employs an array of small laser beams to create many microscopic areas of thermal necrosis within the skin called microscopic treatment zones (MTZ). Even though fractional photothermolysis completely destroys the epidermis and dermis within these MTZ, the 3-dimensional pattern of damage heals quickly and with few side effects. FP is currently used to treat fine wrinkles, photodamaged skin, acne scars, and melasma. Due to its clinical efficacy and limited side effects, fractional photothermolysis has established itself in the past two years as an alternative treatment modality to the conventional ablative and non ablative laser therapy (Laubach & Manstein, 2007).

1.2 Objective

1.2.1 To compare the clinical effectiveness and side effect of fractional Nd:YAG 1064 with those of the low-fluence Nd-YAG 1064 toning laser in treatment of melasma patients by using MASI score.

1.2.2 To compare satisfaction between patients treated with fractional Q-switched 1,064 nm Nd:YAG laser and low-fluence Q-switched 1,064 nm Nd:YAG laser.

1.2.3 To compare the side effects between treatment with fractional Q-switched 1,064 nm Nd:YAG laser and low-fluence Q-switched 1,064 nm Nd:YAG laser.

1.3 Research Hypothesis

Fractional Q-switched 1,064 nm Nd:YAG laser has higher effectiveness and lower side effect than low fluence Q-switched 1,064 nm Nd:YAG laser for the treatment of melasma.

1.4 The Scope of Research

Thirty patients with melasma on both side of cheeks, female, ages 30-65, were randomly assigned to the treatment with fractional Q-switched 1,064 nm Nd:YAG laser and low-fluence Q-switched 1,064 nm Nd:YAG laser on each half of the face. The treatments were performed twice a month for three months at Mae Fah Luang University Hospital, Bangkok. Photograhic documentation used identical camera setting, patient positioning and environmental light by VISIA® Complexion. Analysis system was done before treatment, every four weeks and four weeks after the last treatment. Clinical improvement of MASI score, satisfactions and side effect of treatment were independently evaluated by two masked dermatologists and the patients.

1.5 Conceptual Framework

After occurring of multiple factors such as sunlight, hormones, genetic factor, pregnancy, thyroid dysfunction, cosmetics and medications, melasma is the result of increased deposition of melanin in epidermis and/or dermis. Lasers act disrupting melanin granules in upper dermis, which are subsequently engulfed by the macrophages.

Fractional Q-switched Nd:YAG is currently used to treat melasma. Due to its clinical efficacy and limited side effects. Fractional photothermolysis (FP) has established itself in the past two years as an alternative treatment modality.

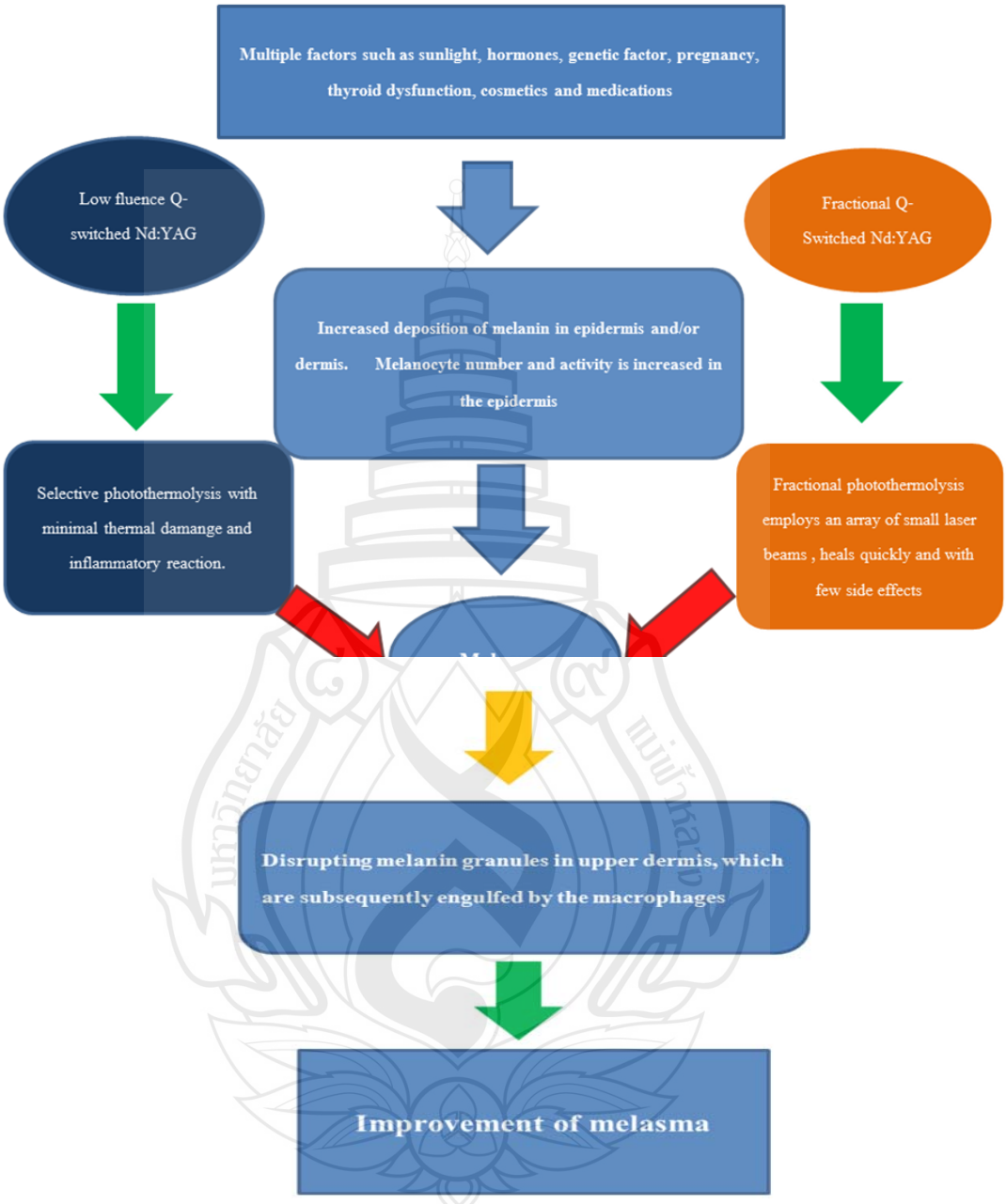


Figure 1.1 Conceptual Framework

1.6 Operational Definition

1.6.1 Melasma is sometimes called *chloasma* appears as a symmetrical blotchy, brownish pigmentation on the face. The pigmentation is due to overproduction of melanin by the pigment cells, melanocytes.

1.6.2 Skin Color – Fitzpatrick Skin Type is an evaluative system that developed by Dr. Thomas Fitzpatrick to assess skin color and a person's tendency to tan or burn. The chart below can be used to determine your Fitzpatrick Skin Type.

Table 1.1 Fitzpatrick Skin Type

Skin Type	Skin Color	C haracteristics
I	White; very fair, red or blonde hair; blue eyes; freckles	Always burns, never tans
II	White, fair, red or blond hair; blue, hazel or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color (common)	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark Brown; mid-eastern skin types	Very rarely burns, tans easily
VI	Black	Never burns, tans very easily

1.6.3 Melasma area and severity index (MASI) is an outcome measurement that developed to provide a more accurate quantification of the severity of melasma and changes during therapy. The MASI score is calculated by subjective assessment of 3 factors: area (A) of involvement, darkness (D), and homogeneity (H), with the forehead (f), right malar region (rm), left malar region (lm), and chin (c), corresponding to 30%, 30%, 30%, and 10% of the total face, respectively.

1.6.3.1 The area of involvement in each of these 4 areas is given a numeric value of 0 to 6 (0 = no involvement; 1 = <10%; 2 = 10%-29%; 3 = 30%-49%; 4 = 50%-69%; 5 = 70%-89%; and 6 = 90%-100%).

1.6.3.2 Darkness and homogeneity are rated on a scale from 0 to 4 (0 = absent; 1 = slight; 2 = mild; 3 = marked; and 4 = maximum).

The MASI score is calculated by adding the sum of the severity ratings for darkness and homogeneity, multiplied by the value of the area of involvement, for each of the 4 facial areas.

1.7 Limitations

1.7.1 Due to the time is limited, so the long term follow-up cannot be achieved.

1.7.2 Limited to biopsy at melasma lesion before and after treatment due to cosmetic concern and patient's consent.

1.8 Expected Benefits and Application

1.8.1 Can provide a benefit in treating melasma.

1.8.2 Can serve as a database for the further study in the future.

CHAPTER 2

REVIEW LITERATURES BACKGROUND AND RATIONAL

2.1 Melasma

Melasma is a common and persistent disorder of hyperpigmentation that affects a significant portion of the population, particularly patients with brownish skin tone. Affected patients often have melasma for many years, and report that the condition has a markedly detrimental effect on their quality of life (Pawaskar et al., 2007). Melasma is seen in both genders and all races, but women of childbearing age are most commonly affected. The exact incidence and prevalence of melasma is unknown, but it is probably more prevalent in people with darker skin (type 4 and 5), especially East Asians.

The Melasma Quality of Life Scale (MELASQOL) has shown that this disorder may have a significant effect on patient quality of life. This is particularly true of facial lesions, which are the primary manifestations of melasma (Pandya, Berneburg, Ortonne & Picardo, 2006). Facial involvement negatively affects a patient's social life, recreation, and emotional well-being, often resulting in psychological disturbances. Given that the clinical assessment of severity by a physician may differ from the patient's perception of severity, this condition may be insufficiently diagnosed or treated (Pawaskar et al., 2007).

Treatment of melasma is often difficult, despite the availability of a range of treatment methods. Lightening agents include retinoic acid (tretinoin) and azelaic acid. Combination therapies such as hydroquinone, tretinoin, and corticosteroids have been used in the treatment of melasma, and are thought to increase efficacy as compared with monotherapy. Kojic acid, isopropylcatechol, N-acetyl-4-cysteaminylphenol, and flavonoid extracts are other compounds that have been investigated for their ability to produce hypopigmentation, but their efficacy, safety, or trial design indicate that the interventions

need further study before they could be recommended. Chemical peels, laser treatments, and intense pulsed light therapy are additional therapeutic modalities that have been used to treat melasma (Gupta, Gover, Nouri & Taylor, 2006).

Of topical therapies, hydroquinone has been considered the gold standard, but recent safety concerns including the risk of exogenous ochronosis or more serious effects due to its cytotoxic effects and its alteration of mitochondrial functioning, have reduced its availability worldwide, despite the lack of clear clinical evidence (Levitt, 2007).

Recently, the 1064-nm Q-switched (QS) neodymium-doped yttrium–aluminium–garnet laser (Nd:YAG) (1064 QNYL) has attracted attention as an alternative treatment method, but the results of this as monotherapy are variable.

2.1.1 Epidemiology

Melasma is common in child-bearing age. Skin types IV through VI, especially Hispanics and Asians, from areas of world with intense sunlight exposure are vulnerable (Sanchez et al., 1981). However, its true incidence is unknown. About 11% of patients developed melasma after using oral contraceptive pills (OCPs). Pregnancy, sun exposure, liver disorder and nutrition are the etiological factors. Prevalence of melasma is found to be higher in darker phototypes. In a study of melasma in Singapore 90% of the patients had skin phototypes III and IV. Melasma was found to be rare in skin-phototypes I and II. Malar pattern has been found to be the most common clinical presentation (Goh & Dlova, 1999).

2.1.2 Clinicopathologic Findings and Diagnosis

The macules of melasma tend to occur in three distinct facial patterns: malar, centrofacial, and mandibular. Although they are usually symmetric, the macules may also be ill-defined, with an irregular border and varied brown to grey color pattern. Beside clinical findings of the history and physical examination, Wood's lamp examination helps distinguish the histologic subtypes.

Three clinical patterns of hyper-pigmentation are recognized in patients with melasma (Sanchez et al., 1981):

1. *Centrofacial*: The macules occupying forehead, cheeks, nose, upper lips and chin

2. *Malar*: The macules are confined to the cheeks and nose

3. *Mandibular*: The macules are seen over the ramus of the mandible

Three histologic patterns have been identified based on the primary location of pigment accumulation (Sanchez et al., 1981):

1. Epidermal pattern shows extra melanin depositing in the basal and suprabasal epidermal layers. Epidermal melasma normally appears light brown and shows enhanced color contrast with Wood's lamp examination.

2. Dermal pattern shows many melanin-laden macrophages in the superficial dermis, often surrounding perivascular spaces. Dermal melasma often appears slightly grey or bluish on gross and with Wood'slamp shows less color contrast.

3. Mixed melasma shows a combination of the two patterns.

Categorization of the type of melasma is useful because it may help guide treatment options and patient expectations since dermal melasma is generally less responsive to therapy, especially topical modalities (Gupta et al., 2006).

2.1.3 Cause of Melasma

Excess melanin in the skin which may occur because of melanocytosis (increased number of melanocytes) or melanogenesis (excess production of melanin) cause the hyperpigmented macules. UV radiation increases levels of dermal stem cell factor and alpha-melanocyte-stimulating hormone in the skin, which may explain the melanocytosis and melanogenesis, respectively (Kang et al., 2006).

Hormonal changes are also important etiologies. Factors such as onset of melasma in pregnancy, increased incidence in women taking oral contraceptive pills or hormone replacement therapy, the histologic finding of high estrogen receptor expression in affected skin, and the strong correlation between estradiol levels and melanogenesis support this conclusion (Lieberman & Moy, 2008). Endocrine organ dysfunction, such as thyroid gland abnormalities, and family history of melasma are also important risk factors (Sialy, Hassan, Kaur & Dash, 2000).

While the exact underlying etiology for melasma remains a mystery. Several well known risk factors are existence. Melasma is more common in darker skin types, particularly Fitzpatrick skin types III and IV. Other risk factors include genetic predisposition, exposure to ultraviolet light, pregnancy, and exogenous

Hormones (for example: oral contraceptives and hormone replacement therapy). A genetic predisposition is suggested by a high reported incidence.

2.1.4 Pathogenesis

The sequence of events in the bio-synthesis of melanin pigment formation namely – migration of the melanoblasts from the neural crest; differentiation of the melanoblasts to form epidermal melanocytes; formation of the tyrosinase and other melanosomal proteins in endoplasmic reticulum; transportation of tyrosinase and melanosomal proteins from the golgi complex to stage I melanosomes; assembly of tyrosinase and melanosomal structure proteins in the formation of the stage II melanosomes within melanocytes; melanisation of melanosomes to form stage 3-4 melanosomes; movement of stage 4 melanosomes from the perikaryon to the dendritic processes of the melanocytes; transfer and incorporation within the keratinocytes; degradation of melanosomes within the keratinocytes and removal of melanin/melanosomes along with loss of stratum corneum (Ortonne, 2012)

The rate limiting catalytic process in the production of melanin is the oxidation of tyrosine by tyrosinase, Raper – Mason pathway .In addition, tyrosinase activity is known to be regulated by fatty acids through ubiquitination. Recapitulation of aforementioned process is the cornerstone in comprehending its etiopathogenesis. Multiple factors namely genetic, sunlight exposure, pregnancy, oral contraceptives, hormone replacement therapy and endocrinological factors are its well-accepted causes (Sanchez et al., 1981). Hepatic disease, cosmetics, drugs, nutritional deficiency and gastro-intestinal disorders have also been incriminated (Bedi & Bhutani, 1975)

2.1.5 Melanogenesis

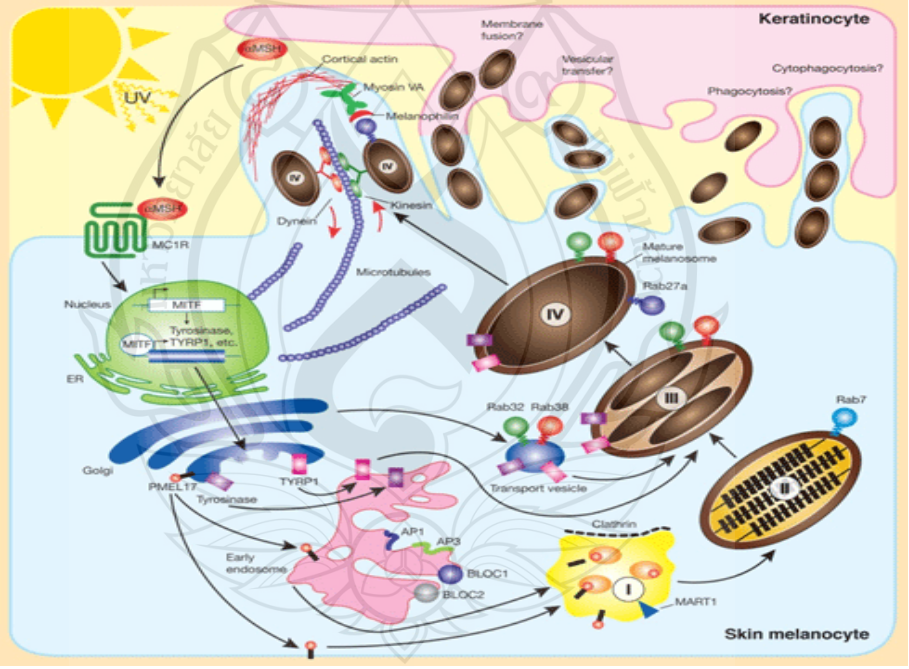
Human skin color stems from in the outermost layer of the skin, the epidermis where the pigment-producing cells melanocytes are localized to produce melanin. Upon exposure of the skin to UV radiation, melanogenesis is enhanced by the activation of the key enzyme of melanogenesis, tyrosinase. Tyrosinase is a glycoprotein located in the membrane of the melanosome, a minifactorial vesicle inside the melanocyte. It has an inner melanosomal domain that contains the catalytic region (approximately 90% of the protein), followed by a short transmembrane domain and a cytoplasmic domain composed of

approximately 30 amino acids. Histidine residues are present in the inner (catalytic) portion of tyrosinase and bind copper ions that are required for tyrosinase activity.

Melanogenesis takes place in the melanosomes. Two types of melanin are synthesized within melanosomes: eumelanin and pheomelanin (Ito, Wakamatsu & Ozeki, 2000).

1. Eumelanin is a dark brown-black insoluble polymer.
2. Pheomelanin is a light red-yellow sulphur-containing soluble polymer.

Tyrosinase catalyses the first two steps of melanin production: the hydroxylation of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA) and the subsequent oxidation of this o-diphenol to the corresponding quinone, L-dopaquinone. Even though L-tyrosine is the building stone for melanin, it can only be transported into the melanosome by facilitated diffusion.



Source GB Health Watch (2013)

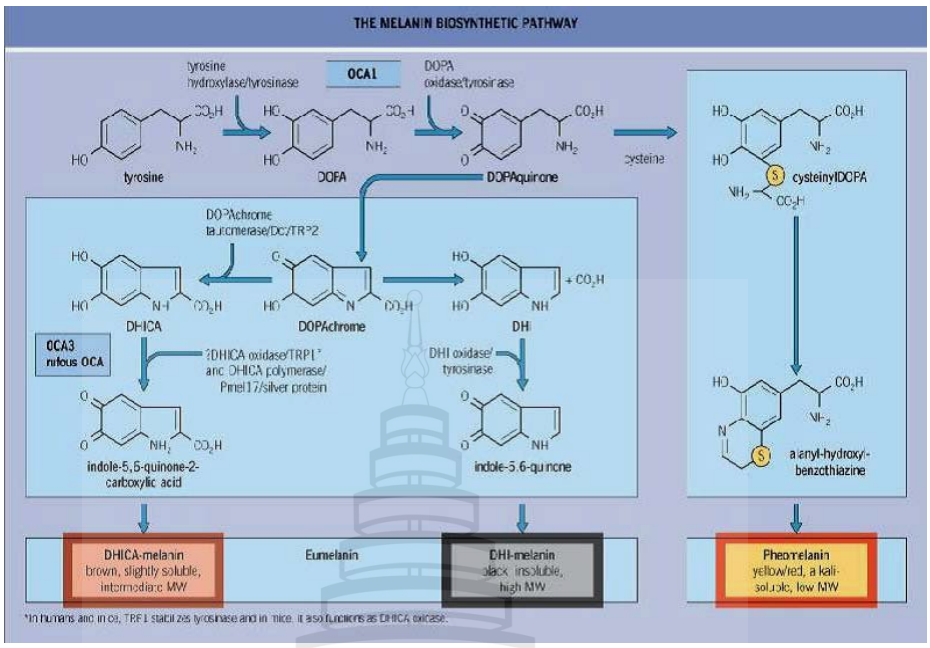
Figure 2.1 Melanogenesis Pathway.

In this context, it is noteworthy that the concentration of L-tyrosine for melanogenesis depends on the conversion of the essential amino acid L-phenylalanine by intracellular phenylalanine hydroxylase (PAH) activity and in contrast to L-tyrosine, L-phenylalanine is actively transported through the melanosomal membrane to ensure high content of L-tyrosine inside this organelle. The importance of L-phenylalanine for melanogenesis is demonstrated in the skin phototypes I–VI where epidermal PAH activities are correlated linearly (Schallreuter & Wood, 1990).

Following the formation of dopaquinone, the melanin pathway is divided into synthesis of the black-brownish eumelanin and red yellow pheomelanin where there is a spontaneous conversion to leucodopachrome and dopachrome. In the eumelanin pathway, dopachrome is either spontaneously converted to 5,6-dihydroxyindole or is enzymatically converted to 5,6-dihydroxyindole-2-carboxylic acid via enzymatic conversion by dopachrome tautomerase (DCT) (Jimbow, Alena, Dixon & Hara, 1992).

Finally, the polymerization of indoles and quinones leads to eumelanin formation. The pheomelanin pathway branches from the eumelanin pathway at the L-dopaquinone step and is dependent on the presence of cysteine which is actively transported through the melanosomal membrane. Cysteine reacts with L-dopaquinone to form cysteinyl-dopa. The latter is then converted to quinoleimine, alanine-hydroxyl dihydrobenzothazine and polymerizes to pheomelanin Tyrosinase can also be indirectly activated by tyrosine hydroxylase isoenzyme 1 (TH1) as it that has been shown to be present in melanosomes and catalyzes L-dopa synthesis. In turn, L-dopa can act as a cofactor for tyrosinase (Prota, 1988).

Redox conditions in the melanosomes are crucial for the balance between the production of eumelanins and pheomelanins. The formation of eu- or pheomelanin is directly determined by reduced glutathione (GSH) (high GSH for eumelanin and low for pheomelanin). Therefore, the expression and functional activity of antioxidant enzymes such as catalase, glutathione peroxidase, glutathione reductase and thioredoxin reductase likely modify the melanogenic pathway (Schallreuter, Lemke, Hill & Wood, 1994).



Source Mosher, Fitzpatrick, Ortonne & Hod (1999)

Figure 2.2 Melanin Biosynthetic Pathway

2.2 Treatment

Because of its refractory and recurrent nature, the goals of treatment often include prevention or reduction in the severity of recurrence, reduction of the affected area, improvement in the cosmetic defect, and reduced time to clearance, all with the fewest possible side effects. The principles of therapy include protection from UV light, inhibition of melanocyte activity and melanin synthesis, and the disruption and removal of melanin granules (Piamphongsant, 1998).

General management recommendations that assist in the clearing of melasma include discontinuation of birth control pills, scented cosmetic products, and phototoxic drugs, coupled with UV protection with use of broad-spectrum (UVA/UVB) sunscreens. Solar exposure exacerbates melasma. Most patients using bleaching agents can expect a recurrence of the disease on exposure to sunlight and artificial UVA and UVB light. This

supports the importance of the use of broad-spectrum sunscreens (SPF 30) in melasma therapies. Broad-spectrum sunscreens must be applied daily throughout the year and continued indefinitely to minimize the reactivation of melanocytes by incidental exposure to the sun (Pathak, Fitzpatrick & Kraus, 1986).

2.2.1 Topical therapies in melasma

2.2.1.1 Hydroquinone is a hydroxyphenolic chemical that inhibits conversion of DOPA to melanin by inhibiting tyrosinase enzyme. It also inhibits deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis in melanocytes and causes degradation of melanosomes and destruction of melanocytes (Jimbow, Obata, Pathak & Fitzpatrick, 1974). It is the most commonly used product in therapy of melasma. Concentrations of HQ in commercially available formulations vary from 2% to 4%; higher concentrations of 6-10% are also prescribed for refractory melasma. Allergic contact dermatitis, nail discoloration, postinflammatory hyperpigmentation (PIH), and depigmentation of surrounding skin are a few of the side-effects of HQ. Exogenous ochronosis following its prolonged use is yet another untoward effect (Engasser & Maibach, 1981).\

2.2.1.2 Azelaic acid. It is a naturally occurring dicarboxylic acid and has shown beneficial results in the treatment of acne and melasma. It has selective cytotoxic effects on hyperactive melanocytes, inhibiting tyrosinase and mitochondrial respiratory enzymes with minimal effects on normally pigmented skin (Baliña & Graupe, 1991).

2.2.1.3 Glutathione. It induces the formation of pheomelanin from dopaquinone, resulting in the reduced formation of eumelanin. *N-acetylcysteine (NAC).* NAC increases glutathione, which stimulates pheomelanin synthesis (Njoo & Westerhof, 1997).

2.2.1.4 Tretinoin. It suppresses melanogenesis nonselectively. It reduces pigmentation by dispersion of pigment granules within keratinocytes, interference of pigment transfer from melanocytes to keratinocytes, and rapid loss of pigment from keratinocytes by acceleration of epidermal turnover. It may also inhibit tyrosinase. Tretinoin is used in a concentration of 0.025 – 0.1%. Cutaneous side-effects were mild irritation, pruritus, erythema, and desquamation (Rendon, Berneburg, Arellano & Picardo, 2006).

2.2.1.5 Topical corticosteroids. They inhibit melanin synthesis through suppression of the general secretory and metabolic activity of the melanocytes without

causing their destruction. Acneiform eruption, telangiectasia, thin skin, and increased thickness of vellus hair were the side-effects (Kanwar, Dhar & Kaur, 1994).

2.2.1.6 Orchid-rich plant extracts including orchid extracts and vitamin C derivative, each to one side of the face. Repeated application was shown that the orchid-rich plant extracts possess efficacy similar to vitamin C derivative in whitening the skin as well as melisma (Tadokoro et al., 2010).

2.2.1.7 Triple combination therapies.

Using of Kligman formula or Kligman recipe, complete depigmentation of the normal skin of adult black males, a formula consisting of 0.1% tretinoin, 5.0% hydroquinone, and 0.1% dexamethasone, in a hydrophilic vehicle. Depigmentation was not attainable when any one of these components was omitted (Kligman & Willis, 1975). Topical corticosteroids alone may exert an antimetabolic effect, resulting in decreased epidermal turnover, and thus, may produce a mild depigmenting effect.

When used in combination with tretinoin and hydroquinone in the treatment of melasma, topical steroid suppresses biosynthetic and secretory functions of melanocytes, leading to early response in melasma. This synergy among the three topical agents, ultimately leads to decreased melanin production over a period of 8 weeks, without any significant side effects. Hence, the rationale seems plausible for its use in melasma.

2.2.2 Chemical Peeling

Chemical peeling or controlled chemical burn, result in destruction of a portion of the epidermis and/or dermis through dry desquamation or moist maceration followed by its exfoliation and subsequent resurfacing of epidermis along with remodeling of collagen, and elastic fibers and the deposition of glycosaminoglycans during the repair process in the dermis (Moy, L. S. & Moy, R. L, 1996). Chemical peels include agents such as GA, TCA, Jessner's solution, salicylic acid (SA), tretinoin, and kojic acid (Ejaz, Raza, Iftikhar & Muzzafar, 2008).

2.2.3 Dermabrasion

It may be performed in recalcitrant cases, but post inflammatory hyper-pigmentation may result in Asian and dark skin. This side effect may be avoided by the

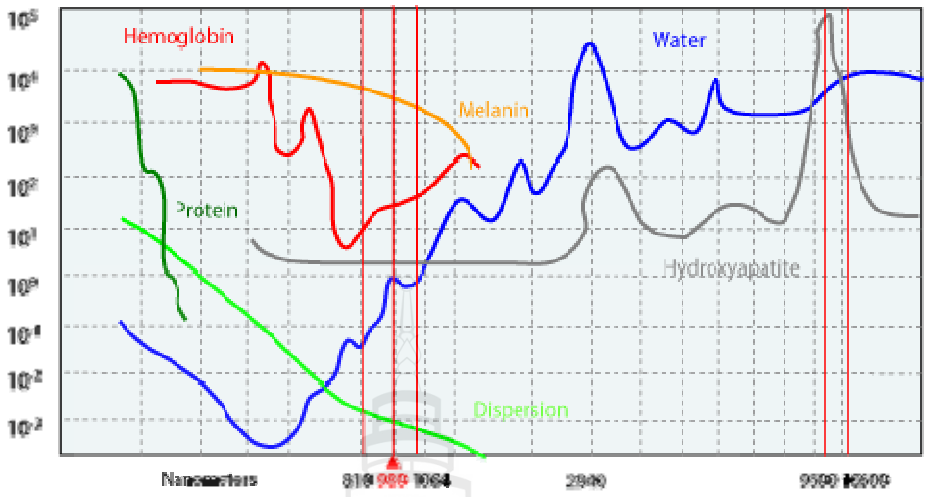
use of micro-dermabrasion technique. Micro-dermabrasion alone or in combination with 15% trichloroacetic acid (TCA), has been found to be an effective, well tolerated treatment for cutaneous hyper-pigmentation (Cotellessa et al., 2003).

2.2.4 Intense pulsed light therapy PIH was observed in patients with mixed melasma, and the majority of patients had mild to moderate pain and burning sensation. However, burns, scarring, and hypopigmentation were not observed. The study concluded that IPL is an effective therapeutic choice for the removal of melanocytic lesions, especially those epidermal in nature; however, long-term

sun protection and bleaching creams should be used after treatment of patients with mixed melasma, because of a higher risk of PIH (Griffiths et al., 1993).

2.2.5 Laser treatment

The use of lasers for the treatment of pigmentary disorders is based on the theory of selective photothermolysis, which proposes that the specific spectrum of light emitted by a particular laser is absorbed selectively by a cell or tissue type (Goldberg, 1997). Pulses of light that are sufficiently brief (i.e., shorter than the thermal relaxation time of melanosomes), and are preferentially absorbed by pigmented structures in tissue, can cause selective heating and thermal damage to the pigmented structures. The choice of wavelength determines depth to which the light will penetrate with sufficient energy density to effect tissue change. If the skin is irradiated with wavelengths in the 400- to 600-nm region, oxyhemoglobin will compete strongly with melanin for absorption of photons and predominately vascular damage will occur. At longer visible wavelengths (600 nm), where absorption by oxyhemoglobin is substantially reduced or absent, absorption by melanin over blood pigments dominates with damage restricted to the melanin pigment-laden structure (Nelson & Applebaum, 1992).



Source Sirona (n.d.)

Figure 2.3 A laser´s Wavelength Determines Many of its Properties and Capabilities because Different Wavelengths are Absorbed by Tissue at Varying Rates

2.2.5.1 Fractional 1550-nm laser. It is recommended to be used judiciously, in view of unacceptable side effects. The efficacy and safety of nonablative 1550-nm fractional laser therapy was assessed and results were compared with those obtained with triple combination therapy in 20 female patients with moderate to severe melasma and Fitzpatrick skin types II – V. The randomized controlled observer blinded study was conducted over 8-week period. The mean treatment satisfaction and recommendation were significantly higher in the laser group at 3 weeks ($p < 0.05$). However, melasma recurred in five patients in both groups after 6 months. Side effects in the laser group were erythema, burning sensation, facial edema, and pain, whereas in the triple group side effects were erythema, burning, and scaling (Kroon et al., 2011).

2.2.5.2 Copper bromide plus/yellow laser (578 nm with 511 nm). It is an antiangiogenic laser which has recently been successfully used for the treatment of melasma specially accompanied by pronounced telangiectasias in Asian skin (Lee et al., 2010).

2.2.5.3 The erbium:YAG laser emits light with 2940-nm wavelength that is highly absorbed by water-containing tissue. This property enables the laser to ablate skin with minimal residual thermal damage, thereby potentially minimizing the risks of PIH. A study by Manaloto and Alster treated 10 patients (skin phototypes II-V) with 3 consecutive full-face passes. Although several properties of the laser are theoretically excellent for cutaneous resurfacing, the resultant inflammatory dermal reaction stimulates the activity of melanocytes in melasma-irradiated skin, leading to temporary worsening of the pigment. However, this study found that any PIH that developed responded well to treatment with peels and topical treatments. The study concluded that erbium:YAG laser resurfacing does effectively improve melasma; however, the almost universal appearance of transient PIH necessitates prompt and persistent intervention. The use of this laser therapy was, thus, recommended only for refractory/recalcitrant melasma (Manaloto & Alster, 1999).

2.2.5.4 A combination of Q-switched alexandrite laser (755 nm) and the carbon-dioxide (CO2) laser in a randomized pilot study containing 8 patients was effective in removing hyperpigmentation as all patients showed complete resolution. The CO2 laser alone seemed less effective as two patients acquired peripheral hyperpigmentation after treatment. This was thought to occur because of the lower energy at the edges resulting in PIH in the areas that had intact melanocytes. Despite this, the study concluded that this laser therapy is safe, as there was no scarring or infection and that the combination of the two laser therapies was effective in removing hyperpigmentation (Nouri, Bowes, Chartier, Romagosa & Spencer, 1999). However, a split-face study of 6 Thai female patients by Angsuwarangsee and Polnikorn found that with one pass of a CO2 laser and then one pass of a Q-switched alexandrite laser, PIH was commonly found in darker skin types. In refractory melasma the combination of CO2 lasers and Q-switched alexandrite laser was unpredictable (Angsuwarangsee & Polnikorn, 2003).

2.2.5.5 The pigmented lesion dye laser (500-520 nm) has been found to be ineffective in the treatment of deep dermal pigmented lesions such as melasma, and PIH. Grekin et al. found that of the 10 patients treated for melasma, 8 did not obtain improvement and minimal lightening was noted in only two. Melasma does not respond

well to this laser, often with hyperpigmentation resulting from treatment (Grekin, Shelton, Geisse & Frieden, 1993).

2.2.5.6 Q-switched ruby laser (694 nm), melasma has a variable response to Q-switched ruby laser (694 nm), and most studies report poor results, with recurrences soon after treatment. Goldberg reported that although patients with fair complexion seem to show a greater response, melasma will often recur, sometimes fairly soon after treatment (Goldberg, 1993). Taylor and Anderson, in a study of 8 patients with melasma (N = 4) or PIH (N = 4), found that this laser treats melasma ineffectively. Irradiation caused a 2-week worsening of pigment, followed by clearing in one patient. However, melasma began to recur after exposure to sunlight. One patient experienced confetti-like hypopigmentation, which lasted 12 months without improvement. One patient showed no change at all, and the fourth patient experienced no change after the first test and worsening of hyperpigmentation after the final testing (Taylor & Anderson, 1994).

2.2.5.7 1064 nm Q-switched Nd:YAG laser has increasingly been referred to as laser toning for nonablative skin rejuvenation and melasma in Asian countries (Wattanakrai, Mornchan & Eimpunth, 2010).

1. Collimated low-fluence Q-switched Nd. YAG Laser has been used in recent years and gained much popularity in Asian countries for nonablative skin rejuvenation and the treatment of melasma (Sim et al., 2014). In laser toning, multiple passes of low-fluence laser (e.g., 1.6–3.5 J/cm2) are delivered through a large spot size (e.g., 6–8 mm) to optimize the energy delivery and to achieve mild erythema, as the clinical end point. The intention is to have multiple laser treatments at subthreshold fluences to potentially obtain clinical improvement with lower down time. Due to minimal down time, some clinicians have proposed daily use of laser toning for skin rejuvenation, while others prefer weekly, bi-weekly, or monthly intervals. This treatment method is a new concept that can be described as selective photothermolysis with minimal thermal damage and inflammatory reaction in the tissues affected by pigmentation. Accordingly, it should be regarded as minimized selective photothermolysis (MSP). Its common adverse effects include pain, erythema, and temporary edema. Rarely, partially hypo-pigmented macules, and diffuse hyper-pigmentation, mottled depigmentation may be encountered.

1064-nm Q-switched Nd:YAG laser's efficacy with low pulse energy was assessed in the treatment of melasma in 25 women by retrospective analysis of clinical photographs and patient satisfaction rates. Follow-up results 2 months after the last treatment, as defined by the grading scale, revealed that, 11 of the 25 patients (44%) had marked clinical improvement: 7 of these (28%) had near-total clinical improvement, 5 had moderate clinical improvement and 2 had minimal to no improvement (Cho, Kim, & Kim, 2009). This data suggests that the use of a Q-Switched Nd:YAG laser with low pulse energy is an effective, easily performed treatment for melasma in selected east Asian patients.

Several investigators reported successful treatment of melasma with the laser toning. Polnikorn presented two cases of refractory dermal melasma in which melasma lesions were successfully resolved with a combination of 1064 nm Q-switched Nd:YAG laser (Medlite C6, HOYA ConBio) and a topical 7% alpha arbutin solution. Two female Asian patients received 10 weekly laser treatments (3.4 J/cm2, 10 Hz, 6 mm spot size, 20 passes in total). Greater than 80% reduction of the epidermal and dermal hyperpigmentation was achieved with no recurrence at 6-month and 1-year follow up (Polnikorn, 2008).

Wattanakrai et al. (Wattanakrai et al., 2010) treated 22 patients with melasma in a split-face trial. They compared combined treatment of sub-thermolytic Q-switched Nd:YAG and 2% hydroquinone with 2% hydroquinone alone. After five weekly treatments, improvement in the relative lightness index was significantly higher in the experiment side (Q-switched Nd:YAG with 2% hydroquinone) than in the control side. Using the same device, Cho et al. treated 25 women with melasma (2.5–5 J/cm2, 6–8 mm spot sizes) and achieved marked clinical improvements in 44% of the patients treated after multiple sessions of treatment (Cho et al., 2009).

The exact mechanism of laser toning on the improvement of melasma is still unclear. It has been proposed that melanin granules are fragmented and dispersed into the cytoplasm without cellular destruction by repetitive laser energy with a subphotothermolytic fluence (<5 J/cm2) over large spot size. Subcellular selective photothermolysis (SSP) describes how laser toning improves melasma lesions. Mun et al. investigated ultrastructural changes in melanocytes and melanosomes after low-fluence Q-switched Nd:YAG laser treatment (7 mm spot size, 1.6–2.0 J/cm2, two passes) in

patients with melasma. The volume of the melanocytes, the number of melanosomes, and connecting melanocytic dendrites were considerably reduced in epidermis after the laser treatment. Because mature melanosomes accumulate in the dendrites of melanocytes, selective photothermolytic effect of the laser can be focused intensively on the dendrites. Therefore, this result can also be interpreted as selective photothermolytic effect of the laser on mature melanosomes. Low-fluence Q-switched Nd:YAG laser treatment achieved selective photothermolytic effect on subcellular-specific organelle melanin (Mun et al., 2011).

2. Fractional resurfacing

Fractional resurfacing is a newer technology that creates microzones of thermal damage. It does not cause full-thickness epidermal wounds, so recovery is more rapid and, theoretically, the resulting inflammation and dyspigmentation is less of a risk. This laser is approved by the FDA for the treatment of melasma, periorbital rhytides, pigmented lesions, skin resurfacing, acne scars, and surgical scars (Rahman, Alam & Dover, 2006). The microthermal zones of injury limit the area of skin that is damaged with each treatment, which may decrease the risk of postinflammatory hyperpigmentation. In addition, the transepidermal elimination of these microthermal treatment zones after injury could serve as an effective method of removing dermal melanophages. However, in certain subgroups of patients, laser toning may worsen melasma.

For such refractory melasma, heat control is essential for successful outcome. Heat as low as 42^{o}C induces melanocyte proliferation and melanogenesis by increasing growth of cell body & dendrites, increasing cell replication, and increasing tyrosinase activity. Heat from various photothermolysis procedures can worsen pigmentary disorders by increasing melanin production and/or stimulating melanin transfer. Fractional beam delivery and lower repetition rate appear to elicit decreased thermal stimulation of melanocytes. Result in heat deposition in deeper dermis far away from epidermal-melanin unit. Less heat at the level of EDJ (Epidermal-Dermal Junction) = Less thermal stimulation of EMU Epidermal-melanin unit = Reduced risk of hyperpigmentation. Fractionated QSNY beams are superior to bulk beams in reducing the risks of hyperpigmentation by significant reduction of thermal stimulation of melanocytes (Nakazawa, Sahuc, Damour, Collombel & Nakazawa, 1998).

Small trial looked at the histopathologic effects of fractional laser technology on melasma. The authors treated 10 patients with epidermal melasma who had Fitzpatrick skin phototypes III to IV every 2 weeks for four sessions. Biopsy specimens were obtained before treatment and 3 months after the final treatment, and they were instructed to avoid depigmenting agents but to use sunscreen. After treatment, lesional skin showed a decrease in the number of epidermal melanocytes and fewer enlarged melanocytes on electron microscopy; however, there was no correlation between histologic improvement and investigator-rated improvement. Importantly, no postinflammatory hyperpigmentation was seen 3 months after therapy was completed (Goldberg, Berlin & Phelps, 2008).

Fractional laser therapy is the only laser treatment for melasma that has been approved by the FDA, and it has shown promising results. Given the risk for hyperpigmentation, some authors suggest using lower fluences, variable pulses, and pretreating all patients with hydroquinone for up to 6 weeks before laser therapy, especially in patients with a history of postinflammatory hyperpigmentation (Rahman et al., 2006).

Melasma lesions can recur or get darkened and rebound hyperpigmentation can occur. Laser toning can also potentially unmask previously subclinical melasma. These complications are probably due to sublethal damage or stimulation of hyperactive melanocytes, which may further increase melanin production and results in hyperpigmentation (Kang et al., 2002). Other complications of laser toning include physical urticaria, acneiform eruption, minute petechiae, whitening of fine facial hair, herpes simplex reactivation, leukoderma, and mottled hypopigmentation (Polnikorn, 2008).

The development of permanent depigmentation after multiple repetitive QS Nd:YAG laser treatments was described by several authors. It is believed that the depigmentation observed after repetitive high-fluence QS Nd:YAG laser is the same entity as leukoderma punctata, which has been reported in patients receiving long-term psoralen and ultraviolet light therapy. The high-cumulative laser fluences used in these studies produce skin inflammation and epidermal disruption that result in a high incidence of pigmentary alteration and rebound melisma (Chan, Ho, Shek, Yeung & Chan, 2010).

In Conclusion Melasma is a common problem worldwide, particularly in females with phototype III-IV skin, and is usually a persistent condition. For most patients, topical skin care regimens are only of limited value, probably because of the high incidence of dermal and mixed-type melasma, which cannot be cleared by suppressing melanogenesis alone. Because melasma is a chronic disorder in most individuals and exacerbations are inevitable, it is important to develop a procedure that is simple to perform, has minimal risks and recovery time, and a high safety and efficacy profile in all skin phototypes. The most practical approach to eliminating dermal melanosomes is with nanosecond-domain lasers because of their selectivity, and of these, the QS Nd:YAG laser appears to have the best suited wavelength; it has a high safety profile in darker phototypes and the capacity for deep dermal penetration. Microdermabrasion plus low-fluence QS Nd:YAG laser treatment is a simple noninvasive procedure with minimal risk and no recovery time and usually induces a rapid remission. Treatment works in all skin phototypes in just 2 to 3 treatment sessions and can produce long-lasting improvement. Histologic assessment of melanocytes and dermal melanosomes after new therapeutic interventions for melasma will help to clarify the mechanism of action and optimize treatment outcomes. Fractional laser therapy appears to be the most promising laser or light treatment for melasma; however, there is still a long-term risk of postprocedure hyperpigmentation and a possible need for maintenance therapy.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Study Design

Randomized split-face controlled trial was conducted to assess the effects of treatment on the appearance of facial melasma.

3.2 Study Population

Patients of Thai nationality, ages 30-65 years old, Fitzpatrick skin types III-V, with facial melasma on both sides of face, who want to treat their melasma at Mae Fah Luang University Hospital, Bangkok.

3.3 Sample Size Determination

In order for the study to be adequate size, relative to the goals and purposes of the study, the sample size must be identified carefully so that an effect of such magnitude as to be of scientific significance will also be statistically significant.

The sample size was calculated from the formula of one sample, using the ratio of measurement from the previous study (Kim et al., 2013).

From the formula

$$n = \frac{2\delta d^2(Z_{\alpha/2} + Z_{\beta})^2}{(\bar{\mu}1 - \bar{\mu}2)^2}$$ 1

Where α = Probability of type I error (2-sided) = 0.05, Z $\alpha/2$ = 1.96

B = Probability of type II error (2-sided) = 0.20, Z_{β} = 0.8416

μ_1 = Mean of mMASI on the side that recieved the 1064 QSNY alone at baseline = 4.35

$\mu 2$ = Mean of mMASI on the side that received the 1064 QSNY alone at 12 weeks follow up = 1.77

SD (Difference) = 1.61

ı = 5

Hence, the number of the sample size in this study was 5 people per group. Since we evaluated by 3 aged group, n= 5x3 = 15, drop out 20% hence, total number of sample size required in this study is 18.

3.4 Selection Criteria

3.4.1 Inclusion Criteria

3.4.1.1 Healthy Thai patients with melasma on both sides of the face who had tried variety of treatments previously and history of refractory melasma.

3.4.1.2 Female, aged 30-65 years old with Fitzpatrick skin types III to V.

3.4.1.3 All subjects were able to participate in the treatment twice a month for the duration of three months and could be followed up at one month after the last treatment.

3.4.1.4 All female of child bearing potential had an acceptable form of birth control during the study.

3.4.1.5 All subjects were required to sign an informed consent form of benefits, risks and possible complications of the treatment and publication of photographs.

3.4.2 Exclusion Criteria

3.4.2.1 Pregnancy and lactation.

3.4.2.2 Medical illness such as poorly controlled diabetic mellitus, coagulopathy, photosensitivity and immunosuppressant.

3.4.2.3 History of poor wound healing, abnormal scarring.

3.4.2.4 Active inflammatory skin disease, open wound in the treatment area.

3.4.2.5 History of malignant or premalignant lesions in the treatment area.

3.4.2.6 Patients who receiving oral pills, hormone replacement therapy, or topical bleaching agents within 1 month or chemical peeling, laser, or IPL within 6 months of enrollment.

3.4.3 Discontinuation Criteria

3.4.3.1 Participant wants to discontinuation the program due to any reason.

3.4.3.2 Participant encounters serious complication from the treatment.

3.4.3.3 Participant receives other treatment for melisma.

3.4.3.4 Pregnancy, serious illness, and dying.

3.4.3.5 Failure in follow up appointment.

3.4.4 Study Location

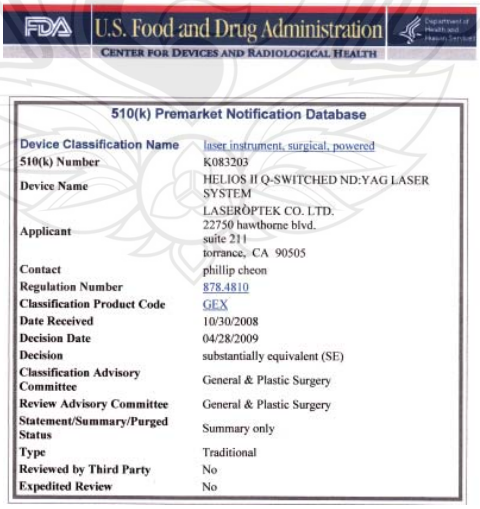
Mae Fah Luang University Hospital, Bangkok.

3.4.5 Intervention

Half of the patient's face was treated with HELIOS.

Figure 3.1 Unique Fractional Q-Switched Nd:YAG Laser (1064 nm/532 nm).

Helios II is the unique fractional Q-Switched Nd:YAG laser (1064nm/532nm) by LASEROPTEK, the spatial distribution of laser beam is designed to be uniform to reduced side effects such as hyperpigmentation or hypopigmentation. Helios II is also designed to keep a stable energy with uniform beam profile during long time operation at maximum repetition rates.



FDA U.S. Food and Drug Administration
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

510(k) Premarket Notification Database

Device Classification Name	laser instrument, surgical, powered
510(k) Number	K083203
Device Name	HELIOS II Q-SWITCHED ND:YAG LASER SYSTEM
Applicant	LASEROPTEK CO. LTD. 22750 hawthorne blvd. suite 211 torrance, CA 90505
Contact	phillip cheon
Regulation Number	878.4810
Classification Product Code	GEX
Date Received	10/30/2008
Decision Date	04/28/2009
Decision	substantially equivalent (SE)
Classification Advisory Committee	General & Plastic Surgery
Review Advisory Committee	General & Plastic Surgery
Statement/Summary/Purged Status	Summary only
Type	Traditional
Reviewed by Third Party	No
Expedited Review	No

Figure 3.2 HELIOS II was approved by US FDA and FDA Thailand.

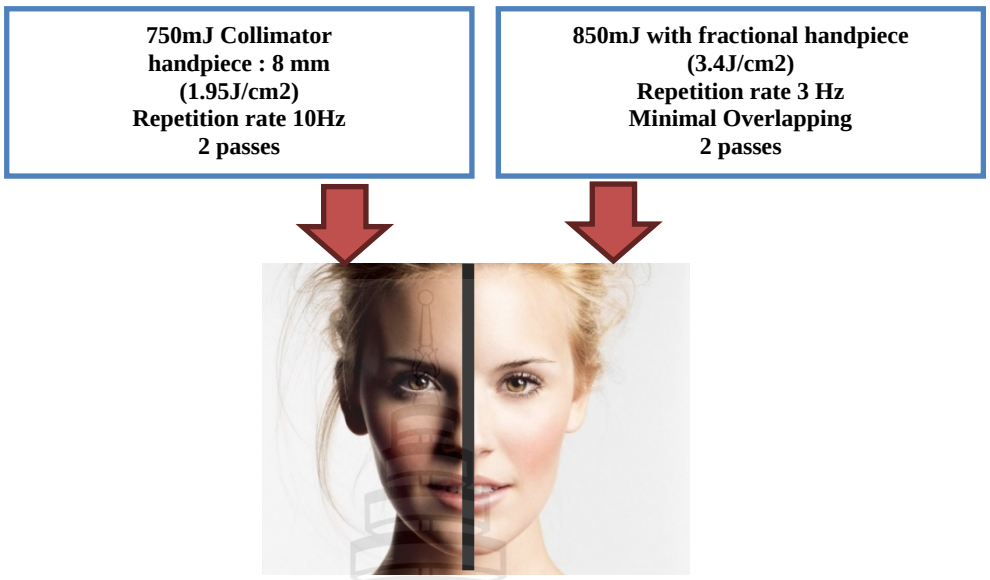


Figure 3.3 Treatment protocol in each side of faces.

Table 3.1 Specifications of HELIOS II.

Laser type	**Nd:YAG**
Wavelength	1064/532 nm
Pulse duration	8 ns
Pulse Energy(max.)	1064nm:1.0J, 532 nm:0.5 J, Quasi-long: 2J
Repetition rates	1-10 Hz
Spot size	Zoom hand piece : 1-7 mm Fractional hand piece : 5x5 mm2 Collimator hand piece : 8 mm
Display	10.4” TFT LCD Touch panel
Electrical control	ARM processor
Cooling system	Closed cycle water to air heat exchanger
Electrical power	220V, 50~60Hz

3.5 Study Procedures

3.5.1 Generate Randomizations Sequence.

The researcher generated randomization which randomly determined which side of the patient's face to be treated with fractional Q-switched 1,064 nm Nd:YAG laser and which side with low-fluence Q-switched 1,064 nm Nd:YAG laser by using random allocation software and conceals the sequence in opaque envelopes.

3.5.2 Preparations of Research Subjects.

3.5.2.1 Patients were selected to enroll in the study according to the selection criteria.

3.5.2.2 The researcher intensively explained the purpose of the research, process during the study, benefits and possible complications of the treatment.

3.5.2.3 The patients signed an informed consent form for participation in the study.

3.5.2.4 The information of the patient was recorded.

3.5.2.5 The researcher selected the randomization sequence envelop.

3.5.3 Treatment process.

3.5.3.1 Before each treatment, the researcher took a photograph of each patient using VISIA® complexion analysis system (Canfield, Fairfield, NJ) of which the following were required:

1. 12 megapixel resolution.
2. Automatic focus.
3. Automated white balance correction.
4. Facial positions : Left 37,Center 0,Right 37.
5. Multi-spectrual Imaging (Standard daylight fluorescent lighting, cross Polarized flash, and ultraviolet lighting).
6. Placing a clear plastic on the border of lesions and marking the reference points.
7. Drawing the lesions on the clear plastic.

8. The marking point of lesion for refer measurement by mexameter was defined.

3.5.3.2 Before the treatment procedure, the treatment areas were cleansed with a mild soap. After that the face was cleansed with 70% alcohol.

3.5.3.3 The researcher did the intervention on each side of the patient's cheek according to the prepared randomized sequence. The treatment was done twice a month for three months consecutively. The device treating each side of the face was the same in all six treatment sessions.

3.5.3.4 The researcher evaluated the patients during the post-treatment about their discomfort (tenderness and burning sensation), erythema, and other side effects.

3.5.3.5 After the treatment, the researcher applied cold compression to relieve the patient's burning sensation.

3.5.3.6 After the burning sensation was relieved, the researcher advised the patient to follow the post-treatment care suggestions.

1. Apply sunscreen with SPF 50 (Ceptaphil® UVA/UVB Defense SPF 50, Galderma) in the morning.

2. Avoid exposure to the sun after the treatment.

3.5.3.7 The patients were given side effect of the treatment. If the patients experienced any severe side effects, they had to go to see the researcher before the next session. The researcher would treat the side effects.

3.5.4 Follow Up

One month after the completion of the 6 sessions, the researcher took a photograph of each patient by using VISIA ® Complexion Analysis System.

3.6 Outcome Measurement and Data Collection

3.6.1 Clinical Evaluation

One doctor performed laser treatment while two other doctors reviewed all cases retrospectively and performed evaluation, while being blinded from any clinical information. Using comparision of the patients' photographs taken by VISIA® to

evaluate the improvement of melasma between before treatment and one month after completing six times treatments by MASI grading scale.

Melasma area and severity index (MASI) is an outcome measurement method that developed to provide a more accurate quantification of the severity of melasma and changes during therapy. Melasma area severity index (MASI) is developed by Kimbrough-Green *et al* for the assessment of melasma. The severity of the melasma in each of the four regions (forehead, right malar region, left malar region and chin) is assessed based on three variables: percentage of the total area involved (A), darkness (D) and homogeneity (H).

A numerical value assigned for the corresponding percentage area involved is as follows:

0 = no involvement
1 = <10% involvement
2 = 10-29% involvement
3 = 30-49% involvement
4 = 50-69% involvement
5 = 70-89% involvement
6 = 90-100% involvement

The darkness of the melasma (D) is compared to the normal skin and graded on a scale of 0 to 4 as follows:

0 = normal skin color without evidence of hyperpigmentation
1 = barely visible hyperpigmentation
2 = mild hyperpigmentation
3 = moderate hyperpigmentation
4 = severe hyperpigmentation

Homogeneity of the hyperpigmentation (H) is also graded on a scale of 0 to 4 as follows:

0 = normal skin color without evidence of hyperpigmentation
1 = specks of involvement
2 = small patchy areas of involvement <1.5 cm diameter
3 = patches of involvement >2 cm diameter
4 = uniform skin involvement without any clear areas

To calculate the MASI score, the sum of the severity grade for darkness (D) and homogeneity (H) is multiplied by the numerical value of the areas (A) involved and by the percentages of the four facial areas (10-30%).

Total MASI score = Forehead 0.3 (D+H)A + right malar 0.3 (D+H)A + left malar 0.3 (D+H)A + chin 0.1 (D+H)A

3.6.2 Patient Assessments

Patients were asked to evaluate the improvement of melasma using the grading scales:

0 = no improvement
1 = < 25% (mild) improvement
2 = 25-50% (moderate) improvement
3 = 51-75% (good) improvement
4 = >75% (excellent) improvement

Patients were asked to evaluate their satisfaction with the treatments using the quartile grading scale:

0 = dissatisfied
1 = less satisfied
2 = moderately satisfied
3 = very satisfied
4 = most satisfied

In order to make measurement of the side effects, the patients were asked to record the following side effects after each treatment:

1. Pain score, ranging from no pain (0) to the most pain(10)
2. Duration (days) of facial erythema
3. Others, such as post-inflammatory hyperpigmentation and hypopigmentation, ulceration, infection and scar formation.

3.7 Data analysis

Significance levels for all analyses were set at p-value < .05

3.7.1 Effectiveness as Evaluated by Dermatologists, The Researcher Did the Following:

3.7.1.1 Calculated the mean of MASI score from the same two dermatologists. Evaluated by VISIA® complexion analysis system.

3.7.1.2 Compared the mean of melanin index improvement scores of the side of the face treated with fractional Q-switched 1,064 nm Nd:YAG laser with the mean of another side treated with low-fluence Q-switched 1,064 nm Nd:YAG laser by using Mexameter. The paired t-test statistics was employed to analyze possible differences.

3.7.1.3 Compared the mean of MASI scores before the treatment with the mean of the scores after the treatment of each treatment mode. The paired t-test statistics was used to evaluate the difference.

3.7.1.4 Compared the mean of MASI scores after the treatment between two treatments. The paired t-test statistics was used to evaluate the difference.

3.7.1.5 Compared the mean of MASI scores reduction after completing the treatment between two modes. The paired t-test statistics was used to evaluate the differences.

Researcher also investigated further by applying age-related analysis on both MASI scores and mean melanin index. By doing so, the subjects were categorized into three age groups (Age 30-40, Age 41-55 and Age 56-65) and researcher did the following:

3.7.1.6 Calculated the mean of MASI score from the same two dermatologists for each age group. Evaluated by VISIA® complexion analysis system.

3.7.1.7 For each age group, compared the mean of melanin index improvement scores of the side of the face treated with fractional Q-switched 1,064 nm Nd:YAG laser with the mean of another side treated with low-fluence Q-switched 1,064 nm Nd:YAG laser by using Mexameter . One-way ANOVA test statistics was employed to analyze possible differences.

3.7.1.8 For each age group, compared the mean of MASI scores before the treatment with the mean of the scores after the treatment of each treatment mode. One-way ANOVA test statistics was employed to analyze possible differences.

3.7.1.9 For each age group, compared the mean of MASI scores after the treatment between two treatments. One-way ANOVA test statistics was employed to analyze possible differences.

3.7.1.10 For each age group, compared the mean of MASI scores reduction after completing the treatment between two modes. One-way ANOVA test statistics was employed to analyze possible differences.

3.7.2 Patient Assessment

The researcher compared the mean of satisfaction scores of the side of the face treated with fractional Q-switched 1,064 nm Nd:YAG laser with the mean of another side treated with Low-fluence Q-switched 1,064 nm Nd:YAG laser. The Wilcoxon Signed Ranks test statistics was being used to evaluate the difference.

3.7.3 Measurement of Side Effects

The researcher compared the means of side effects between after the treatment with fractional Q-switched 1,064 nm Nd:YAG laser and after the treatment with low-fluence Q-switched 1,064 nm Nd:YAG laser. McNemar test for significance changes was used to evaluate the difference between 2 groups.

CHAPTER 4

RESULTS

4.1 General Characteristics of the Sample

Demographic information of eighteen female patients aged between 30-65 year old who had melasma on faces were recruited from the outpatient department (OPD), Mae Fah Luang University Hospital as well as from local and internet advertisement. The diagnosis of melasma was based on clinical features by physician and Wood's lamp is being used to confirm and evaluate type of melasma.

Details of the demographic data are shown in Table 4.1

Table 4.1 General Demographic Data

Demographic data	Subjects (n = 18)	
	Number	Percentage
Gender		
Male	0	0.00
Female	18	100.00
Age		
Mean ± S.D.	47.28 ± 10.71 years	
Minimum – Maximum	32 – 65	
Occupations		
Officer	7	38.89
Government officer	6	33.33
Housewife	4	22.22
Business owner	1	5.56
Mean melasma duration	6.17±4.36	

Table 4.1 (continue)

Demographic data	Subjects (n = 18)	
	Number	**Percentage**
Fizpatrick skin type		
Type 3	5	27.78
Type 4	13	72.22
Types of melisma		
Epidermal	2	3.33
Dermal	4	22.22
Mixed	12	66.67
Pattern of melisma		
Malar	11	61.11
Centrofacial	3	16.67
Mandibular	4	22.22
Family history		
No	8	44.44
Yes	10	55.56
Aggravating factors		
Sunlight	18	100.00
Make-ups	3	16.67
Hormone	3	16.67
Pregnancy	2	11.11

Table 4.1 demonstrated the demographic data of the subjects. The mean age of the subject was 47.28 ± 10.71 years, and the mean duration of melasma was 6.17±4.36 years. Majority of the subjects had Fitzpatrick skin type IV (13/18), while the rest were type III (5/18). Nearly 67% (12/18) of the subjects had mixed type and Malar pattern was found most common. Around 55.56% of the subjects had family history of melasma. For the aggravating factors such as sunlight all subjects (18/18) were exposed.

4.2 Clinical Evaluation

Among eighteen subjects, all subjects had completed the six sessions of treatments. Melasma area severity index (MASI) score and adverse effects were recorded quad-weekly. Treatment was stopped at 12 weeks and subjects were followed-up 4 weeks after treatment. Final MASI score and adverse effects were noted at the end of follow-up period. Mean MASI scores were compared using paired sample t-test and one-way ANOVA.

4.2.1 Clinical Evaluation by Dermatologists

Grading from the two physicians was calculated to get MASI score grade after treatment, result as shown in table 4.2.

Table 4.2 MASI scores evaluated by 2 physicians at baseline and 4th week

Number of Subject	MASI					
	Baseline			4th week		
	Doctor1	Doctor2	Mean	Doctor1	Doctor2	Mean
1	13	12	**12.5**	12.3	12.3	**12.3**
2	15.2	14.6	**14.9**	12.3	11.4	**11.85**
3	12	13	**12.5**	9.6	9.6	**9.6**
4	13	13.2	**13.1**	9.3	8.1	**8.7**
5	10.5	10	**10.25**	13	10.8	**11.9**
6	14.5	15.6	**15.05**	15.6	13.2	**14.40**
7	23	24	**23.5**	21	21	**21.0**
8	16.2	15.6	**15.9**	13.5	13.5	**13.5**
9	22.2	24	**23.1**	17.8	17.8	**17.8**
10	22.5	20	**21.25**	22.5	15.6	**19.05**
11	15.5	13	**14.25**	12	11.4	**11.7**
12	12	12	**12.0**	5.4	5.4	**5.4**
13	11	13.2	**12.1**	6.8	6.8	**6.8**

Table 4.2 (continued)

Number of Subject	MASI					
	Baseline			4th week		
	Doctor1	Doctor2	Mean	Doctor1	Doctor2	Mean
14	21.6	21.6	**21.6**	13.2	15.9	**14.55**
15	15.5	14.5	**15.0**	13	13	**13.0**
16	18.2	16.5	**17.35**	13.2	13.2	**13.2**
17	10	9.8	**9.9**	6	8.1	**7.05**
18	16.5	15.5	**16.0**	13	13	**13.0**
Mean ± S.D.			**15.57 ± 4.23**			**12.49 ± 4.13**

Table 4.3 MASI scores evaluated by 2 physicians at 8th week and 12th week

Number of Subject	MASI					
	8th week			12th week		
	Doctor1	Doctor2	Mean	Doctor1	Doctor2	Mean
1	10.8	10.8	**10.8**	9.4	9.4	**9.4**
2	10.6	10.6	**10.6**	8.6	9.3	**8.95**
3	9	9	**9.0**	9	8.1	**8.55**
4	4.8	4.8	**4.8**	3.6	3.6	**3.6**
5	9.6	9.6	**9.6**	8.1	7.2	**7.65**
6	13.2	12	**12.6**	12	10	**11.0**
7	15.9	16.2	**16.05**	13.2	14.4	**13.8**
8	10.8	10.8	**10.8**	8.7	7.9	**8.3**
9	13.2	13.2	**13.2**	12	10	**11.0**
10	17.8	15.5	**16.65**	13.2	11	**12.1**
11	9.6	9.6	**9.6**	7.2	8.1	**7.65**
12	3.6	3.6	**3.6**	3.6	4.8	**4.2**
13	3.6	5.4	**4.5**	4	5.4	**4.7**
14	12	12	**12.0**	8.7	8.7	**8.7**
15	9.3	9.3	**9.3**	6	6.8	**6.4**

Table 4.3 (continued)

Number of Subject	MASI					
	8th week			12th week		
	Doctor1	Doctor2	Mean	Doctor1	Doctor2	Mean
16	8.1	8.1	**8.1**	5.4	4.8	**5.1**
17	5.4	5.4	**5.4**	4.8	4.8	**4.8**
18	9.6	9.6	**9.6**	5.4	6	**5.7**
Mean ± S.D.			**9.79 ± 3.66**			**7.87 ± 2.90**

Table 4.4 MASI scores evaluated by 2 physicians at 16th week

Number of Subject	MASI		
	16th week		
	Doctor1	Doctor2	Mean
1	10.8	10.8	**10.8**
2	10.6	10.6	**10.6**
3	9	9	**9.0**
4	4.8	4.8	**4.8**
5	9.6	9.6	**9.6**
6	13.2	12	**12.6**
7	15.9	16.2	**16.05**
8	10.8	10.8	**10.8**
9	13.2	13.2	**13.2**
10	17.8	15.5	**16.65**
11	9.6	9.6	**9.6**
12	3.6	3.6	**3.6**
13	3.6	5.4	**4.5**
14	12	12	**12.0**
15	9.3	9.3	**9.3**
16	8.1	8.1	**8.1**
17	5.4	5.4	**5.4**
18	9.6	9.6	**9.6**
Mean ± S.D.			**10.49 ± 3.81**

Table 4.5 Comparison of MASI scores between each periods and baseline

Comparison of MASI Score	Mean	S.D.	p-value
4th week – Baseline	-3.08	2.17	< 0.001*
8th week – Baseline	-5.78	2.76	< 0.001*
12th week – Baseline	-7.70	5.96	< 0.001*
16th week – Baseline	-5.08	3.38	< 0.001*

Note. *p*-value compared between 2 groups with paired t-test, *Significant at $p < 0.05$

The results showed that there was constant decrease on MASI scores after each treatment interval during the course of 12 weeks treatment. The results were shown in table 4.5, the comparison of mean MASI scores between each periods and baseline after treatment also showed statistical significant difference ($p < 0.05$).

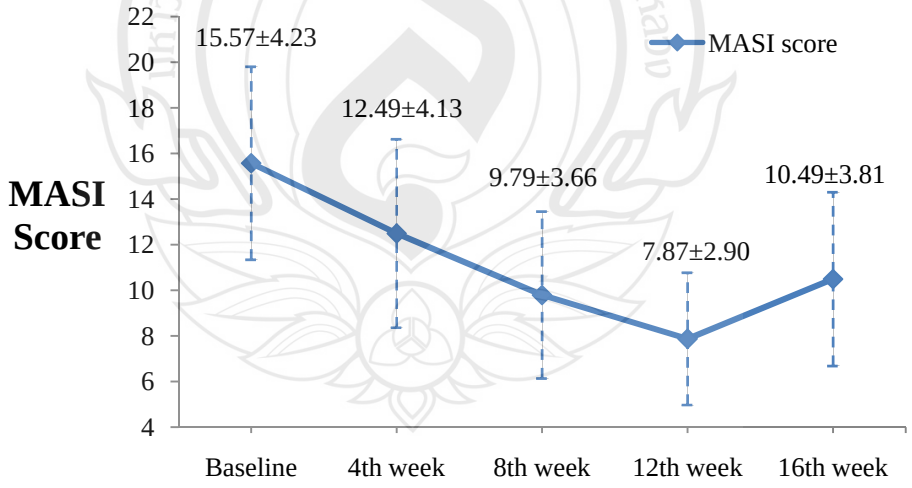


Figure 4.1 Linear graph showed comparison of MASI scores in each visit

As shown in figure 4.1 when comparing the mean MASI score at baseline which was 15.57 ± 4.23, the mean MASI score on 4th week after treatment was decreased to 12.49 ± 4.13 and then further decreased to 9.79 ± 3.66 and 7.87 ± 2.90 on 8th and 12th week after treatment respectively. The follow up result after treatment was stopped on 16th week showed that the mean MASI score was increased to 10.49 ± 3.81, but still significantly lower than the mean MASI score before recorded treatment at baseline.

4.2.2 Improvement of Melanin index

Melanin index of the patients were evaluated by Mexameter before treatment, at 4th, 8th, 12th and 16th week of treatment.

Table 4.6 Mean melanin Index Evaluated by Mexameter® of Each Visit in Collimator

Mean Melanin Index (n = 18)					
Number of patient	**Collimator**				
	Base line	**4th week**	**8th week**	**12th week**	**16th week**
1	153	168	154.54	139	148
2	311	296	282.33	260	273.33
3	227	210	173	156	196
4	245	234	232	220.65	238
5	303	289	266	253.2	271
6	337	325	311	312	321
7	222	215	206	195	210.43
8	193	187	153	145	181.34
9	395	373	324	296	322
10	279	255.32	243.54	238.2	248
11	280.53	260	242	235	245
12	358	324.73	321.76	313	324
13	272.43	241	231	226	235
14	209	191	191	181	197.43
15	207	178	166	152	150
16	242	229	210	202.34	208
17	235	224	174	167	170
18	210.76	184	183.96	164	196.54

Table 4.7 Mean Melanin Index Evaluated by Mexameter® of Each Visit in Fractional

Mean Melanin Index (n = 18)					
Number of patient	**Fractional**				
	Baseline	**4th week**	**8th week**	**12th week**	**16th week**
1	159	154	148.43	135	142.64
2	275	307	197	258.3	186.67
3	192	176	160	154	152
4	263	245.76	215	202.5	223
5	296	270.54	263.96	253.2	265
6	330	320	312	306.2	313.76
7	197	204.65	187	176.3	189.32
8	225	201	180	145	190
9	451	401	380	360	389
10	277	288.12	262	246.76	265
11	313.54	271	258	232	262
12	388	364.87	349	321.65	331
13	332	289.65	259	223	257
14	185	177	175	167.43	176.33
15	230	224	173	168.65	194.26
16	266	254	245	234.9	248
17	209	170	151	152	160
18	193	177	176.31	156.87	177

Table 4.8 Statistical analysis of mean melanin index in each visit between collimator and fractional

Mean Melanin Index	Collimator (n=18)	Fractional (n=18)	Paired Difference	p-value
Baseline	259.98 ± 62.60	265.64 ± 76.98	-5.66 ± 30.10	0.436
4th week	243.56 ± 58.08	249.76 ± 70.69	-6.20 ± 28.13	0.363
8th week	225.84 ± 56.67	227.32 ± 68.56	-1.48 ± 30.88	0.842
12th week	214.19 ± 56.82	216.32 ± 66.07	-2.13 ± 19.87	0.655
16th week	229.73 ± 55.87	229.00 ± 67.64	0.73 ± 34.63	0.930

Note. *p*-value compared between 2 groups with paired t-test

Table 4.8 showed statistical analysis of mean melanin index in each visit between collimator and fractional before the treatment, at 4th, 8th, 12th and 16th week of treatment.

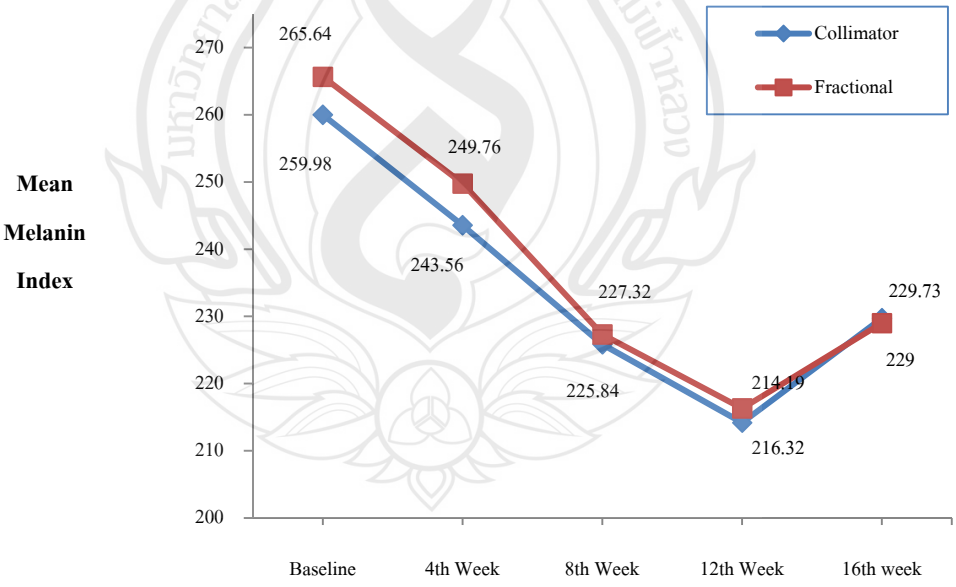


Figure 4.2 Linear graph showed comparison of means melanin index in each visit between side performed collimator and fractional

When comparing the mean melanin index score at baseline (collimator /fractional) was (259.98/265.64), at 4th week after treatment mean melanin index (collimator/fractional) was decreased to (243.56/249.76), the mean melanin index (collimator/fractional) was further decreased to (225.84/227.32) and (214/19/216.32) in 8th and 12th week after treatment, respectively.

The follow up result after treatment on 16th week showed that the mean melanin index (collimator/fractional) was rebounded to (229/229.73), but still significantly lower than the mean melanin index before recorded treatment at baseline.

The aforementioned results showed no statistical significant difference ($p > 0.05$) between comparison of mean melanin index between collimator and fractional after treatment. The data showed that there was constantly decreased melanin index after each treatment interval in both collimator and fractional sides.

Table 4.9 Statistical analysis of difference of mean melanin index in each visit with baseline between collimator and fractional

Group Comparison	Collimator (n=18)	Fractional (n=18)	Paired Difference	p-value
4th week - baseline	-16.43 ± 11.27	-15.89 ± 20.62	-0.54 ± 21.07	0.915
8th week - baseline	-34.14 ± 17.33	-38.32 ± 23.26	4.18 ± 19.39	0.373
12th week - baseline	-45.80 ± 82.73	-49.32 ± 92.61	3.53 ± 30.37	0.629
16th week - baseline	-30.26 ± 19.70	-36.64 ± 23.59	6.38 ± 20.79	0.210

Note. *p*-value compared between 2 groups with paired t-test

As shown in table 4.9, there was constantly decreased melanin index after each visit as compared to Baseline. However, results from the statistical analysis of difference of mean melanin index in each visit with baseline between collimator and fractional showed no statistical significant difference ($p>0.05$).

Even though figure 4.2 indicated that the overall mean melanin index on the side treated by collimator during each visit was relatively lower than side treated by fractional,

the results on table 4.9 revealed better overall clinical response to fractional treatment rather than collimator. The result also showed lower melanin index on the side treated by fractional during the follow-up on 16th week after treatment which indicated the lower rate of melanin reoccurrence.

Table 4.10 Age-related analysis of mean melanin index in side treated by collimator in each visit

Groups of comparison	Mean Melanin Index (Collimator)				
	Baseline	**4th week**	**8th week**	**12th week**	**16th week**
Age 30-40	255.50±85.59	244.00±31.84	227.48±66.19	223.48±65.96	223.63±68.80
Age 41-55	268.78±50.82	248.33±22.47	237.49±47.55	237.03±62.43	244.33±47.25
Age 56-65	255.67±57.24	238.34±19.56	212.55±62.43	183.06±27.57	221.22±57.11
p-value	**0.924**	**0.961**	**0.768**	**0.227**	**0.757**

Note. *p*-value compared 3 groups with One-way ANOVA test, *Significant at $p < 0.05$

Table 4.11 Age-related analysis of mean melanin index in side treated by fractional in each visit

Groups of comparison	Mean Melanin Index (Fractional)				
	Baseline	**4th week**	**8th week**	**12th week**	**16th week**
Age 30-40	262.50±101.73	256.07±86.94	216.74±83.08	218.20±66.13	220.82±86.33
Age 41-55	274.92±67.86	250.87±59.98	240.71±54.26	246.95±82.42	241.85±54.48
Age 56-65	259.50±70.93	242.33±75.62	224.50±75.99	183.80±35.73	224.33±69.49
p-value	**0.942**	**0.950**	**0.843**	**0.267**	**0.862**

Note. *p*-value compared 3 groups with One-way ANOVA test, *Significant at $p < 0.05$

Table 4.10 and 4.11 showed age-related analysis of mean melanin index in side treated by collimator and fractional in each visit of the patients. There was no statistical significant difference (p<0.05) in the age-related analysis of mean melanin index in side treated by collimator and fractional in each visit.

Results showed that there was constant decrease in melanin index after each treatment interval in both collimator and fractional sides for the age group of 56-65. Whereas for age group 30-40 and Age group 41-55, the melanin index tend to decrease on 4th and 8th week, but was, in most cases, rebounded slightly on 12th week (except for Age group 41-55 treated by collimator where melanin index on 8th and 12th week tend to be the same).

Although it would be interesting to see what was the cause of this rebound occurred on the age Group 30-40 and age group 41-55 subjects receiving collimator and fractional treatment, the research on how such change in melanin index occurred lie beyond the scope of this thesis.

Table 4.12 Age-related analysis of difference of mean melanin index from baseline in side treated by collimator in each group comparison

Groups of comparison	**Mean Melanin Index (Collimator)**			
	4th week - Baseline	**8th week - Baseline**	**12th week - Baseline**	**16th week - Baseline**
Age 30-40	-11.50±15.18	-28.02±25.53	-32.03±84.50	-31.87±28.67
Age 41-55	-20.45±7.48	-31.29±9.08	-31.75±104.89	-24.46±11.75
Age 56-65	-17.33±9.82	-43.12±11.64	-73.61±61.09	-34.43±17.19
p-value	**0.401**	**0.300**	**0.629**	**0.687**

Note. p-value compared 3 groups with One-way ANOVA test, *Significant at p < 0.05

Table 4.13 Age-related analysis of difference of mean melanin index from baseline in side treated by fractional in each group comparison

Groups of comparison	Mean Melanin Index (Fractional)			
	4th week - Baseline	**8th week - Baseline**	**12th week - Baseline**	**16th week - Baseline**
Age 30-40	-6.43±27.18	-45.76±29.41	-44.30±95.84	-41.69±29.75
Age 41-55	-24.05±15.48	-34.21±24.98	-27.97±120.04	-33.08±25.59
Age 56-65	-17.17±16.66	-35.00±15.81	-75.69±64.49	-35.17±17.45
p-value	**0.349**	**0.658**	**0.689**	**0.823**

Note. *p*-value compared 3 groups with One-way ANOVA test, *Significant at $p < 0.05$

Table 4.12 and 4.13 showed age-related analysis of difference of mean melanin index from baseline in side that was treated by collimator and fractional respectively in each age group comparison. The result showed that was no statistical significant difference ($p<0.05$) in the age-related analysis of difference of mean melanin.

Results showed that collimator treatment was the best overall clinical response ,by looking at melanin index, for age group 30-40 and age group 41-55 on 12th week. Although table 4.12 revealed that the largest decrease of melanin index did happen on the data recorded on 8th week of the treatment. For age group 56-65, the best clinical response was on 12th week after receiving the treatment.

For fractional treatment, the best overall clinical response by looking at melanin index was on the 8th week after treatment for age group 30-40 and age group 41-55. For age group 56-65, the best clinical response was on 12th week after receiving the treatment.

Follow-up result on 16th week for both collimator and fractional treatments showed that the mean melanin index (collimator/fractional) was increased, especially for age group 56-65 which rebounded significantly, but still considerably lower than the mean melanin index before recorded treatment at baseline.

Table 4.14 Age-related analysis comparing difference of mean melanin index from baseline between the side were treated by collimator and fractional in each age-group

Groups of comparison	*p*-value compared Mean Melanin Index (Collimator v.s. Fractional)		
	Age 30-40	**Age 41-55**	**Age 56-65**
4^{th} wk – Baseline	0.680	0.534	0.987
8^{th} wk – Baseline	0.094	0.696	0.147
12^{th} wk – Baseline	0.376	0.777	0.882
16^{th} wk – Baseline	0.423	0.237	0.933

Note. *p*-value compared 2 groups with paired t-test, *Significant at $p < 0.05$

Table 4.14 showed comparison of difference of mean melanin index from baseline between the side treated by collimator and fractional to age-related in each visit. There was also no statistical significance at $p < 0.05$.

Table 4.15 Age-related analysis of mean MASI scores in each visit

Groups of comparison	Mean MASI scores				
	Baseline	**4^{th} week**	**8^{th} week**	**12^{th} week**	**16^{th} week**
Age 30-40	17.02±4.97	14.11±4.47	10.79±3.78	8.19±2.51	11.52±3.67
Age 41-55	14.88±3.90	12.06±2.84	9.65±2.86	9.51±3.48	10.90±2.63
Age 56-65	14.82±4.16	11.30±4.99	8.93±4.58	5.90±1.51	9.07±5.01
p-value	**0.619**	**0.504**	**0.699**	**0.086**	**0.540**

Note. *p*-value compared 3 groups with One-way ANOVA test, *Significant at $p < 0.05$

Table 4.15 showed age-related analysis of mean MASI scores in each visit**.** There was no statistical significance of mean MASI scores when compare to age-related.

The result from table 4.15 also revealed that there was constant decrease on MASI scores after each treatment interval for all age groups during the course of 12 weeks treatment. MASI scores were rebounded after treatment is stopped on 16th week, but still significantly lower than the mean MASI score before recorded treatment at baseline.

Table 4.16 Age-related analysis of difference of mean MASI scores in each visit

Groups of comparison	Mean MASI scores			
	4th week - Baseline	**8th week - Baseline**	**12th week - Baseline**	**16th week - Baseline**
Age 30-40	-2.91±1.81	-6.23±2.96	-8.83±7.06	-5.50±3.61
Age 41-55	-2.82±3.13	-5.23±3.32	-5.37±6.78	-3.98±3.38
Age 56-65	-3.52±1.66	-5.89±2.35	-8.92±3.97	-5.75±3.49
p-value	**0.849**	**0.833**	**0.531**	**0.644**

Note. *p*-value compared 3 groups with One-way ANOVA test, *Significant at $p < 0.05$

Table 4.16 showed age-related analysis of difference of mean MASI scores from in each visit. There was no statistical significance of mean MASI scores when compared to age-related. The result also revealed that there was constant decrease on MASI scores after each treatment interval for all age groups during the course of 12 weeks treatment. Treatment was most effective on 12th week for all age group with highest decreased MASI scores on age group 56-65. MASI scores were rebounded after treatment was stopped on 16th week, but still considerably lower than the mean MASI score before recorded treatment at baseline.

Table 4.17 Patient satisfaction scores after treatment on 16th week in sides performed collimator and fractional

Patient Satisfaction Scores					
Number of patient	**Collimator**	**Fractional**	**Number of patient**	**Collimator**	**Fractional**
1	4	3	10	4	4
2	4	4	11	4	4
3	4	4	12	3	3
4	2	3	13	3	3
5	4	4	14	4	4
6	4	4	15	3	3
7	3	4	16	2	2
8	4	3	17	3	4
9	4	4	18	4	4

Table 4.18 Statistical analysis of patient satisfaction scores after treatment on 12th week in sides performed collimator and fractional

	Patient Satisfaction Scores (Percent) (n=18)	
	Collimator	**Fractional**
4 = Most satisfied	11 (61.1)	11 (61.1)
3 = Very satisfied	5 (27.8)	6 (33.3)
2 = Moderately satisfied	2 (11.1)	1 (5.6)
1 = Less satisfied	-	-
0 = Not change	-	-
-1 = Dissatisfied	-	-
Mean ± S.D.	3.50 ± 0.71	3.56 ± 0.62
Median (Min-Max)	4 (2-4)	4 (2-4)
P-value	0.655	

Note. *p*-value compared between 2 groups with Wilcoxon Signed Ranks test

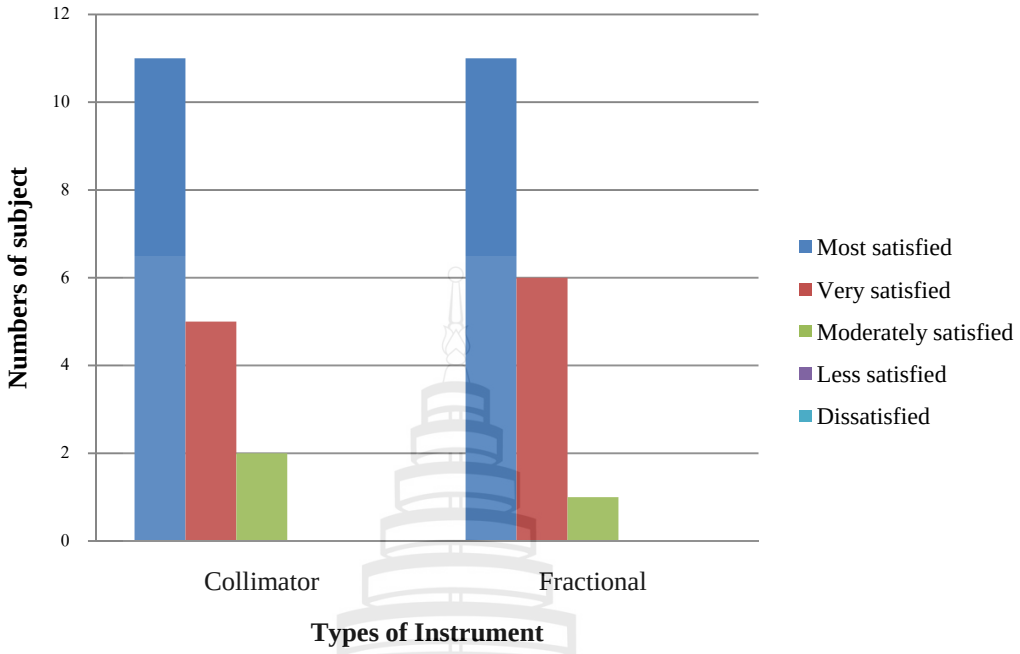


Figure 4.3 Bar chart showed the numbers of subject divided by patient satisfaction score in sides performed collimator and fractional after treatment on 12th week

According to table 4.11 and figure 4.3, after being treated with collimator mode, eleven patients (61.1%) rated their satisfaction as most satisfied. Five patients (27.8%) rated as very satisfied. The rest (11.11%) rated as the moderately satisfied. After being treated with fractional mode, eleven patients (61.1%) rated their satisfaction as most satisfied. Six patients (33.3%) rated their satisfaction as very satisfied. And the rest (5.6%) rated as the moderately satisfied.

4.3 Side Effects

Treatment-related adverse events were occurred in 3 patients treated by collimator group and 1 patient treated by fractional group. Only minimal post-operative reactions, such as erythema, scaling and edema, were detected. McNemar test for significance changes was used to evaluate the difference between 2 groups, there was no statistic significant (p-value = 0.625).

CHAPTER 5

DISCUSSION AND CONCLUSION

Melasma is a common and persistent disorder of hyperpigmentation. The main pathology is caused by increased number of melanocytes and increased activity of melanogenic enzymes. Melanin is the insoluble, submicrometer intracellular pigments that absorbs light at a wide range of wavelengths – from 250 to 1,200 nm. The use of lasers for the treatment of pigmentary disorders is based on the theory of selective photothermolysis, which proposes that the specific spectrum of light emitted by a particular laser is absorbed selectively by a cell or tissue type (Goldberg, 1997). The rate of local heating and rapid material expansion can be so severe that structures are torn apart by shock waves, cavitation, or rapid thermal expansion. The cracked particles are phycocyted by the macrophages.

Based on our clinical study, 18 Thai women were treated twice a month for 12 weeks with a 1064 nm Q-switched Nd:YAG laser. The mean age of the subject was 47.28 ± 10.71 years, and the mean duration of melasma was 6.17±4.36 years. Majority of the subjects had Fitzpatrick skin type IV (13/18), while the rest were type III (5/18). Nearly 67% (12/18) of the subjects had mixed type and Malar pattern was found most common. Around 55.56% of the subjects had family history of melasma. For the aggravating factors such as sunlight all subjects (18/18) were exposed.

There was constantly decreased MASI scores after each treatment interval during the course of 12 weeks treatment (15.57±4.23 at baseline, 12.49±4.13 at 4^{th} week, 9.79±3.66 at 8^{th} week, 7.87±2.9 at 12^{th} week and 10.49±3.81 at 16^{th} week). The follow up result after treatment is stopped on 16^{th} week shows that the mean MASI score is increased but still significantly lower than the mean MASI score before recorded treatment at baseline as the result showed 32.6% reduction from baseline MASI. Both patients and investigators noted similar (50–74%) improvement. Result of melanin index

in both collimator and fractional 1064 nm Q-switched Nd:YAG laser shows similar trend as the MASI. However, results from the statistical analysis of difference of mean melanin index in each visit with baseline between collimator and fractional showed no statistical significant difference. We are not surprised about the results. Due to the basic knowledge, two modalities use the same source of the laser beam and Q-switch mechanism that causes the energy depositing in the same level of tissue depth. The fractional laser was designed to split the laser beam into small hundreds or thousands laser beam causing numerous microscopic treatment zone. The smaller region of treatment caused small region of tissue damage, so more energy to keep optimal temperature in the treatment was slightly higher than in collimated laser. In this research laser protocol, fractional laser used only 3 Hz of repetition rate to causing energy density at 3.4 J/cm^2 that was higher than collimated laser (energy density 1.95J/cm^2 with repetition rate at 10 Hz). Due to the maintaining of intervening normal healthy tissue, lower complication with maintaining high energy density was result. There is no difference in the total energy in both treatment regions, so the treatment result revealed no significant difference.

Source Lapidoth, Yagima Odo & Odo (2008)

Figure 5.1 Fractional Laser Creates Microscopic Treatment Zone

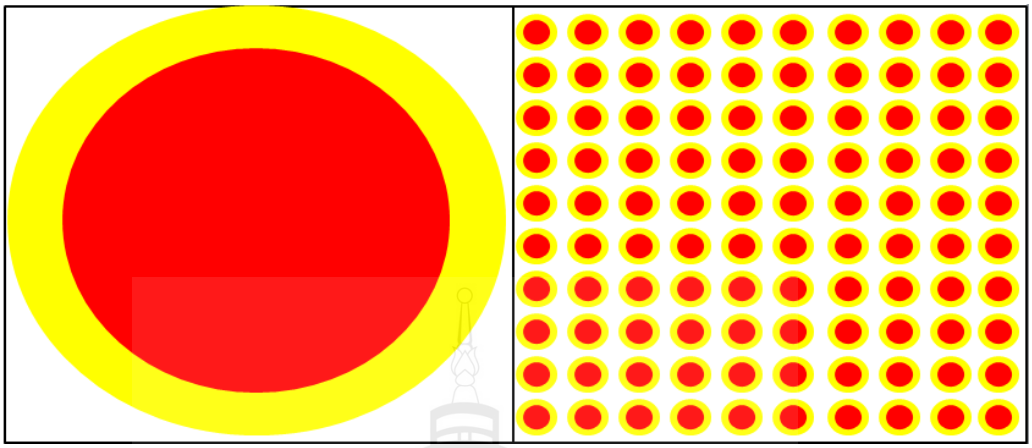


Figure 5.2 Comparing between treatment zone of collimated laser and microscopic treatment zone of fractional laser.

Several investigators also reported successful treatment of melasma with 1064 nm Q-switched Nd:YAG laser: laser toning.

Polnikorn (Polnikorn, 2008) presented two cases of refractory dermal melasma in which melasma lesions were successfully resolved with a combination of 1064 nm Q-switched Nd:YAG laser (Medlite C6, HOYA ConBio) and a topical 7% alpha arbutin solution. Two female Asian patients received 10 weekly laser treatments (3.4 J/cm2, 10 Hz, 6 mm spot size, 20 passes in total). Greater than 80% reduction of the epidermal and dermal hyperpigmentation was achieved.

Author/year	Type of study	No. of patient/ skin type	Type of melasma	Laser	Sittings/ interval	Dose	Assessment	Results	Side effects
Nuttha, 2014 (This study)	RCT*, split face	18/III-IV	Epiderma/dermal/mixed	Colimator QS-Nd:YAG 1064 nm	6/2 weeks	Spot size: 8 mm Fluence: 1.92 J/cm2 Freq: 10 Hz	Objective	Significant improvement in all patient	Erythema, scaling, oedema
				Fractional QS-Nd:YAG 1064 nm		Fluence: 3.4 J/cm2 Freq: 10 Hz Overlapping 2 pass			No side effect
Wattanakrai, 2010	RCT, split face	20/II-V	Dermal/Mixed	QS-Nd:YAG 1064 nm + 2% HQ[1]	5/1 week	Spot size: 6 mm Fluence: 3.0-3.8 J/cm^2 Freq: 10 Hz	Objective	Excellent (76-100): 73% Good (51-75%): 18% Fair (26-50%): 9% Poor (0-25): 0%	Erythema, burning, mottled hypopigmentation (3 pts) Recurrence, rebound hyperpigmentation (18%)
				2% HQ				Excellent: 0% Good: 18% Fair: 32% Poor: 50%	
Polnikorn, 2010		35	Refractory/dermal/mixed	QS-Nd:YAG 1064 nm + topical 7% alpha arbutin	10/1 week → 2/1 month	Spot size: 6 mm Fluence: 3.0-3.4 J/cm^2 Freq: 10 Hz	Subjective	>81%: 30% 51-80: 37% 26-50: 23% 0-25%: 3%	Mottling hypopigmentation (8%) Recurrence (6%) Whitening of fine hair Erythema, discomfort
Choi, 2010		20/III-IV	Facial melasma	QS-Nd:YAG 1064 nm	5/1 week	Spot size: 6 mm Fluence: 3.0-3.4 J/cm^2 Freq: 10 Hz	Objective	Significant improvement in all patients, decreased wrinkling	No side effects
Jeong, 2010	RCT, split face, crossover	13/III-IV		QS-ND:YAG 1064 nm→TCC[1] TCC→QS-Nd:YAG 1064 nm		Spot size: 7 mm Fluence: 1.6-2.0 J/cm^2	Objective	Better results when laser treatment was preceded by TCC	Laser→pain, erythema TCC→aggravation of melasma
Chan, 2010		5		QS-Nd:YAG 1064 nm	9-50	Spot size: 6-8 mm Fluence: 1.6-3.5 J/cm^2	Subjective only	None of the patients improved	Mottled depigmentation
Park, 2011	RCT, split face	16		QS-Nd:YAG 1064 nm		Spot size: 6 mm Fluence: 3.0-2.3 J/cm^2 Freq: 10 Hz	Objective	32.6% improvement is pigmentation	
				QS-Nd:YAG 1064 nm + peels		30% GA[7]		22% improvement in pigmentation	Erythema, burning, oedema
Zhou, 2011		50		QS-Nd:YAG 1064 nm	9/1 week	Spot size: 6 mm Fluence: 2.5-3.4 J/cm^2 Freq: 10 Hz	Subjective only	35.8% improvement	Localized wheal, purpura, recurrence
Suh, 2011		23		QS-Nd:YAG 1064 nm	10/1 week	Spot size: 4, 6, 8 mm Fluence: 2.0-4.0 J/cm^2 Freq: 10 Hz Pulse duration: 5-7 ns	Objective	Significant improvement	Erythema, PIH[8] (3 pts), hypopigmentation (1 pt)
Polnikorn, 2008	Case report	2/III-IV	Refractory, dermal	QS-Nd:YAG 1064 nm		Spot size: 6 mm Fluence: 3.0-4.0 J/cm^2 Freq: 10 Hz	Objective	80% improvement	
Brown, 2011		20/II-IV		QS-Nd:YAG 1064 nm	8/1 week	Spot size: 8-10 mm Fluence: 2.0-4.0 J/cm^2 Freq: 10 Hz	Objective		

*RCT: Randomized controlled trial, [1]HQ: Hydroquinone, [1]TCC: Triple combination cream, [7]GA: Glycolic acid, [8]PIH: Postinflammatory hyperpigmentation

Figure 5.3 Summary of Study Using QS-Nd:YAG (1064nm) Laser for Melasma

Wattanakrai et al. (Wattanakrai et al., 2010) treated 22 patients with melasma in a split-face trial. They compared combined treatment of sub-thermolytic Q-switched Nd:YAG and 2% hydroquinone with 2% hydroquinone alone. After five weekly treatments, improvement in the relative lightness index was significantly higher in the experiment side (Q-switched Nd:YAG with 2% hydroquinone) than in the control side.

Using the same device, Cho et al. treated 25 women with melasma (2.5–5 J/cm2, 6–8 mm spot sizes) and achieved marked clinical improvements in 44% of the patients treated after multiple sessions of treatment (Cho et al., 2009).

While Brown et al. treated 20 subjects with A 1064-nm, Q-switched laser (Focus Medical, Bethel, CT). It was used to deliver 2 – 4 J/cm^2 with 8 – 10 mm spot sizes. Patients with Fitzpatrick type II skin were treated with 3 – 4 J/cm^2 while those with skin types II – IV were treated with 2 – 3 J/cm^2. The mean MASI scores progressively improvement. Scores at baseline, 4 weeks (second treatment) and 8 weeks were significant improvement. Photographs were evaluated by two blind assessors which revealed 19 subjects showing improvement with lightening of their melasma between 25% and 100% (Brown, Hussain & Goldberg, 2011).

More recently Sim et al. treated 50 patients with melasma underwent 15 weeks of weekly treatments, using a Q-switched Nd:YAG laser (RevLite®; HOYA ConBio®, Freemont, CA, USA) at 1064 nm with an 8-mm spot size, and a fluence of 2.8 J/cm^2. Patients and investigators subjectively evaluated the intensity of pigmentation after completion of 15 weekly treatments. Both patients and investigators rated the treatment outcome as “good improvement” on average with improvement rate of 50-74%. None of the 50 patients showed any signs of severe side effects during the course of the treatment (Sim et al., 2014).

For result after treatment on the follow-up on 16th week showed that the mean melanin index (collimator/fractional) was rebounded but still lower than the mean melanin index before recorded treatment at baseline as the results showed 11.63% and 13.79% reduction from baseline melanin index for collimator and fractional treatment accordingly.

For recurrence after complete sessions also found 50 patients were recruited for this study (47 female; 3 male). All were treated using the 1,064-nm QS Nd:YAG laser at low energy levels weekly for nine sessions. Follow-up was done 3 months after the final laser session, and recurrence rates were evaluated. They found that mean MASI scores decreased 61.3% after therapy (from 10.6-4.1, $p<.001$); 70% of patients had more than a 50% decrease in their MASI values. Recurrence rate at the 3-month follow-up was 64% (Zhou, Gold, Lu, & Li, 2011).

Same results as Wattanakrai et al. found that all of patients had recurrence of melasma at 12 weeks follow-up after the last sessions. They concluded that QS-Nd:YAG laser treatment produced only temporary improvement (Wattanakrai et al., 2010).

Brown et al. also reported that all actually worsened because of a vacation to South America where inadequate photoprotection was used. At 1 month follow, up subjects' results were maintained. Evidence of melasma flare was common at 3 months the last treatment (Brown et al., 2011).

Even though, Polnikorn's study reported 2 female Asian patients received 10 weekly laser treatments (3.4 J/cm^2, 10 Hz, 6 mm spot size, 20 passes in total). Greater than 80% reduction of the epidermal and dermal hyperpigmentation was achieved with no recurrence at 6-month and 1-year follow up (Polnikorn, 2008) . But the 1,064-nm QS Nd:YAG laser was combined with 7% arbutin, so the inhibition of the melanocytes might be retained for a longer period of time. Recurrence of melasma may be prevented by combining topical or oral therapy during and after QS Nd:YAG laser therapy.

Clinically, the rebound on both MASI and mean melanin index which reflected the recurrence of melasma was encountered in the majority of both patient groups at 4weeks follow-up. Although there was not yet a clear understanding of the mechanism underlying melasma, the current knowledge suggested that it was a chronic process. As such, lasers could at best be expected to provide temporary improvement in the appearance of melasma. Melasma was defined by chronic overproduction of melanin. The current procedures were not designed to completely halt the production of melanin, but rather to eliminate existing melanin particles, either by targeting them directly (Q-switched lasers), or by opening channels or triggering inflammatory clearance mechanisms involved in wound healing process, in the hopes that the debris wound be eliminated. Hence, the procedures were used by definition meant only to decrease an amount of melanin. As such, these procedures could be predicted to have time-limited benefits; melanin reaccumulation was inevitable so long as the process of melasma was present.

Since side effects of laser toning for skin rejuvenation and melasma treatment were not fully investigated, hence, the treatment outcomes of melasma were considered to be inconsistent and unpredictable with laser and light therapy (Angsuwarangsee et al., 2003) (Wattanakrai, Mornchan & Eimpunth, 2004; Rokhsar**,** Fitzpatrick**,** 2005; Y. H. Li

et al., 2008; Lee et al., 2009). Melasma lesions could recur or get darkened and rebound hyperpigmentation. The laser toning could also potentially unmask previously subclinical melasma (Sim et al., 2013). These complications and drawbacks were probably due to sublethal damage or stimulation of hyperactive melanocytes, which may further increase the melanin production and ultimately result in hyperpigmentation (Kang et al., 2002). Other complications of laser toning could also be expected including physical urticaria, acneiform eruption, minute petechiae, whitening of fine facial hair, herpes simplex reactivation, leukoderma, and mottled hypopigmentation (Polnikorn, 2008). This study also closely monitored all patients for aforementioned as well as other side effects, the observation results showed minimal post-operative reaction such as erythema, scaling and edema; 3 pateints in the collimated laser toning group and 1 pateint in the fractional laser group could be due to maintaining mechanism of intervening zones of healthy tissue in fractional laser but no statistic significant in both group is found. No sign of severe side effects, such as post-inflammatory hyperpigmentation or mottled hypopigmentation, was observed in this study.

Further investigation between the efficacy of the therapy and factors such as age, years of disease according to our study, was done but no statistically significant relationship was found. It seen that these factors did not significantly influence the response of melasma in Thai women, although this remained to be further proved in a larger sample study.

The main limitations of this study were: (1) a small number of included patients; (2) laser settings that may have been suboptimal (3) short term follow up. The initial good results were seen at the short-term follow-up. However, pigmentation could potentially be worsened during the course of time due to melasma's nature of chronic process. No significant differences were found between the two groups on longer follow-up and the results at 4-week follow-up were worsening than 12^{th} week. Interestingly, in spite of this overall outcome, all patients who had treatment would recommend this to their friends and colleagues. Most of the patients also observed the benefits of improvement in skin texture and lightened skin color. Textural changes such as this are thought to be the result of collagen remodeling and are the basis of improvement seen with treatment of photoaged skin.

In conclusion, the treatments used in this study proved to be the safe treatment options for patients with melasma, including those with darker skin types. Patients considered laser therapy to be satisfactory and recommendable. It may be a useful alternative when topical bleaching is ineffective or not tolerated. In future studies a larger cohort of patients should be recruited to better compare treatment outcomes in epidermal and dermal melasma. Moreover, given the high recurrence rate and the absence of major side effects, optimization of laser parameters and long-term maintenance treatment with a bleaching regimen should be considered in future research. Clinical improvement was both subjectively and objectively verified. Because treating melasma with low-fluence 1064 nm Q-switched Nd:YAG laser is relatively simple and noninvasive, it does not affect patients' daily life activities, hence, proved to be suitable option for periodic melasma treatment.

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APPENDICES

APPENDIX A

หนังสือให้ความยินยอมเข้าร่วมในโครงการวิจัย

เขียนที่ ……..……..

วันที่…….……..

ข้าพเจ้า……..……อายุ……ปี

อยู่บ้านเลขที่…..…ถนน…….....หมู่ที่…….…แขวง/ตำบล……..……..

เขต/อำเภอ …..…….…..... จังหวัด…….…….....รหัสไปรษณีย์.....

ขอทำหนังสือนี้ให้ไว้ต่อหัวหน้าโครงการวิจัยเพื่อเป็นหลักฐานแสดงว่า

ข้อ 1. ข้าพเจ้าได้รับทราบโครงการวิจัยของแพทย์หญิงนัฏฐา มีสุนทร และผู้ช่วยศาสตราจารย์แพทย์หญิง สุนิสา ไทยจินดา เรื่อง การศึกษาเปรียบเทียบผลของการใช้เครื่องเลเซอร์เอ็นดี: แย้ก แบบแฟรกชั่น นอลคิว สวิตช์ เทียบกับเครื่องเลเซอร์เอ็นดี : แย้ก พลังงานต่ำ ในการรักษาฝ้าบนใบหน้าในหญิงไทย (A Comparative study of Fractional Q-switched Nd:YAG laser versus Low-fluence Q-switched Nd:YAG laser for facial melasma in Thai females)

ข้อ 2. ข้าพเจ้ายินยอมเข้าร่วมโครงการวิจัยนี้ ด้วยความสมัครใจ โดยมิได้มีการบังคับขู่เข็ญ หลอกลวงแต่ประการใดและจะให้ความร่วมมือในการวิจัยทุกประการ

ข้อ 3. ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยเกี่ยวกับวัตถุประสงค์ของการวิจัย วิธีการวิจัย ประสิทธิผล ความปลอดภัย อาการหรืออันตรายที่อาจเกิดขึ้น รวมทั้งประโยชน์ที่จะได้รับจากการวิจัยโดยละเอียดแล้ว จากเอกสารคำอธิบายโครงการวิจัย

ข้อ 4. ข้าพเจ้าได้รับการรับรองจากผู้วิจัยว่าจะเก็บข้อมูลส่วนตัวของข้าพเจ้าเป็นความลับจะเปิดเผยเฉพาะผลสรุปv การวิจัยเท่านั้น

ข้อ 5. ข้าพเจ้าได้รับทราบจากผู้วิจัยแล้วว่า หากมีอันตรายใด ๆ อันเกิดขึ้นจากการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการรักษาพยาบาลจากคณะผู้วิจัย โดยไม่คิดค่าใช้จ่ายและจะได้รับค่าชดเชยรายได้ที่เสียไปในระหว่างการรักษาพยาบาลดังกล่าว

ข้อ 6. ข้าพเจ้าได้รับทราบในการติดต่อกับ แพทย์หญิงนัฏฐา มีสุนทร หัวหน้าโครงการวิจัย ด้วยหมายเลขโทรศัพท์ 086-563-1626 แล้ว

ข้อ 7. ข้าพเจ้าได้รับทราบแล้วว่าข้าพเจ้ามีสิทธิ์จะบอกเลิกการร่วมโครงการวิจัยนี้ และการบอกเลิกการร่วมโครงการวิจัย จะไม่มีผลกระทบต่อการดูแลรักษาโรคที่ข้าพเจ้าจะพึงได้รับต่อไป

ข้อ 8. แพทย์หญิง นัฏฐา มีสุนทร หัวหน้าโครงการวิจัย ได้อธิบายเกี่ยวกับรายละเอียดต่าง ๆของโครงการตลอดจนประโยชน์ของการวิจัยรวมทั้งความเสี่ยงและอันตรายต่าง ๆ ที่อาจจะเกิดขึ้นใน การเข้าร่วมโครงการนี้ ให้ข้าพเจ้าทราบและตกลงรับผิดชอบตามคำรับรองในข้อ 5 ทุกประการ

ข้าพเจ้าได้อ่านและเข้าใจข้อความตามหนังสือนี้โดยตลอดแล้ว เห็นว่าถูกต้องตามเจตนาของข้าพเจ้า จึงได้ลงลายมือชื่อไว้เป็นสำคัญพร้อมกับหัวหน้าโครงการวิจัยและต่อหน้าพยาน

ลงชื่อ ..... ผู้ยินยอม
(.....)

ลงชื่อ ..... หัวหน้าโครงการวิจัย
(แพทย์หญิง นัฏฐา มีสุนทร)

ลงชื่อ ..... พยาน
(.....)

ลงชื่อ ..... พยาน
(.....)

หมายเหตุ

กรณีผู้ยินยอมตนให้ทำวิจัย ไม่สามารถอ่านหนังสือได้ ให้ผู้วิจัยอ่านข้อความในหนังสือให้ความยินยอมนี้ให้แก่ผู้ยินยอมตนให้ทำวิจัยฟังจนเข้าใจแล้ว และให้ผู้ยินยอมตนให้ทำวิจัยลงนาม หรือพิมพ์ลายนิ้วหัวแม่มือรับทราบ ในการให้ความยินยอมดังกล่าวด้วย

APPENDIX B

แบบบันทึกข้อมูลโครงการวิจัย

<u>แบบบันทึกข้อมูลโครงการวิจัย</u>

เรื่อง การศึกษาเปรียบเทียบผลของการใช้เครื่องเลเซอร์เอ็นดี: แย้ก แบบแฟรกชั่นนอลคิวสวิตช์ เทียบกับการใช้เครื่องเลเซอร์เอ็นดี: แย้ก แบบคิวสวิตซ์พลังงานต่ำในการรักษาฝ้าบนใบหน้าผู้หญิงไทย อย่างเดียว: การศึกษานำร่อง

เลขที่แบบบันทึกข้อมูล.....

ข้อมูลทั่วไปของผู้ป่วย (Patient demographic information)

เฉพาะเจ้าหน้าที่

1. วัน เดือน ปี ที่เก็บข้อมูล..... Date
2. ชื่อ นามสกุล..... Name
3. บ้านเลขที่..... Address

   เบอร์โทรศัพท์..... Tel
4. เพศ 1.ชาย .....2. หญิง Sex
5. อายุ .....ปี Age
6. อาชีพ .....1. ข้าราชการ .....2. พนักงาน Occupation

   .....3. แม่บ้าน .....4. นักเรียน/นักศึกษา

   .....5. กิจการส่วนตัว .....6. อื่น ๆ
7. ระยะเวลาที่เป็นฝ้า (ปี)…… Duration
8. ประวัติคนในครอบครัวเป็นฝ้า FH

   .....1. มี . .....2. ไม่มี
9. ปัจจัยกระตุ้นที่ทำให้เกิดฝ้า Aggravate

   .....1. ตั้งครรภ์

   .....2. การได้รับฮอร์โมน

   ....ยาเม็ดคุมกำเนิด .....รักษาอาการวัยทอง

   ....ฮอร์โมนไทรอยด์ ..... อื่น ๆ (โปรดระบุ.....)

   .....3. การได้รับแสงแดด

   .....4. การใช้เครื่องสำอาง

.....5. ยากันชัก

.....6. ยาที่มีปฏิกิริยากับแสง

10. ประวัติการรักษาที่เคยได้รับมาก่อน Prev Tx

.....1. เคย .....2. ไม่เคย

11. ชนิดของฝ้าจำแนกด้วยการตรวจ wood's lamp

……1. Epidermal type

…….2. Mixed type(epidermal-dermal) type

…….3. Dermal type

12. จำแนกชนิดของฝ้าตามบริเวณที่เป็น Pattern

…….1. Centrofacial type

……..2. Malar type

……..3. Mandibular type

13. จำแนกชนิดของสีผิวตาม Skin type …….I…….II……III…...IV……V…….VI Skin type

แบบบันทึกผลการทดลอง

การประเมินประสิทธิภาพการรักษา

1. MASI score =…….

Melasma area (A)

Area (A)	Forehead (f) 30%	Malar (m) Right 30%	Malar(m) Left 30%	Chin (c) 10%
None = 0				
0%-9% = 1				
10%-29% = 2				
30%-49% = 3				
50%-68% = 4				
70%-89% = 5				
90%-100% = 6				

Homogeneity(H)

Homogeneity(H)	Forehead(f) 30%	Malar (m) Right 30%	Malar (m) Left 30%	Chin (c) 10%
Absent = 0				
Slight = 1				
Mild =2				
Marked = 3				
Maxinum =4				

Darkness (D)

Darkness (D)	Forehead (f) 30%	Malar(m) Right 30%	Malar (m) Left 30%	Chin (c) 10%
Absent = 0				
Slight = 1				
Mild = 2				
Marked = 3				
Maximum = 4				

2. Melanin index (MI) by Mexameter MX 18

Melanin Index (Right side)				
baseline	**4th week**	**8th week**	**12th week**	**16th week**

Melanin Index (Left side)				
baseline	**4th week**	**8th week**	**12th week**	**16th week**

3. Global satisfactory โดยผู้เข้าร่วมวิจัย

คะแนนความพึงพอใจในการรักษา : กรุณาวงกลมตัวเลขตามความเป็นจริง

* คะแนนความพึงพอใจในการรักษา มีค่าตั้งแต่ -1 ถึง +4

โดยที่ -1 คือ แย่ลง, 0 คือ ไม่ได้ผล, +1 คือ ดีขึ้นน้อยมาก (1-25%), +2 คือ ดีขึ้นน้อย (26-50%), +3 คือ ดีขึ้นปานกลาง (51-75%), +4 คือ ดีขึ้นมาก (76-100%)

แบบประเมินผลข้างเคียง

1. การประเมินผลข้างเคียงโดยผู้ป่วย

….. 1. มี ..... 2. ไม่มี

ผลข้างเคียง	ไม่มีเลย (1)	น้อยมาก (2)	ค่อนข้างน้อย (3)	ปานกลาง (4)	ค่อนข้างมาก (5)	มากที่สุด (6)
แสบร้อน						
คัน						
แดง						
อาการจุดเลือดออก						
ลอก,แห้ง						

อื่น ๆ .....

2. โดยแพทย์ (Physician evaluation)

…. .. 1. Yes ..... 2. No

Adverse effects	Mild	Moderate	severe
Erythema			
Scaling			
Edema			
Pin point bleeding			
Crusting			
Erosions			

Other……

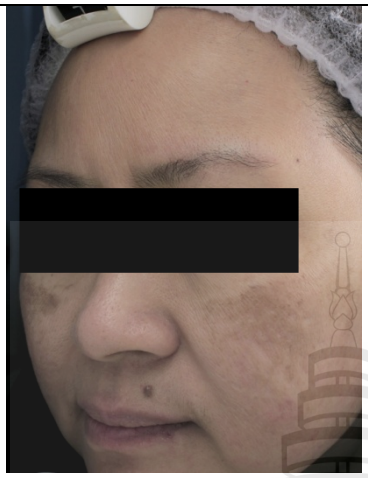
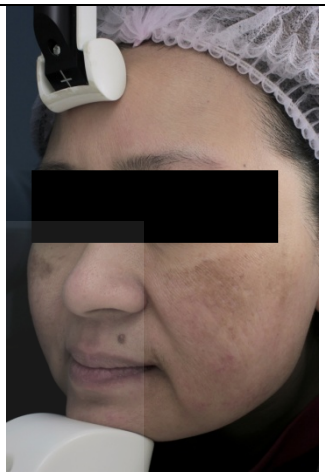
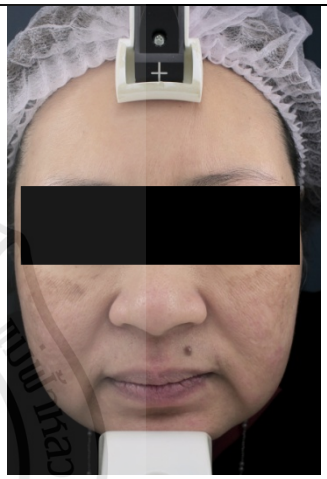
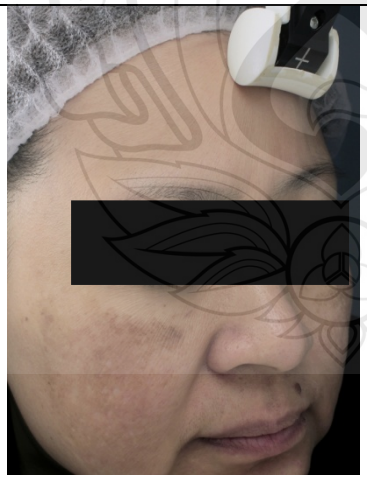
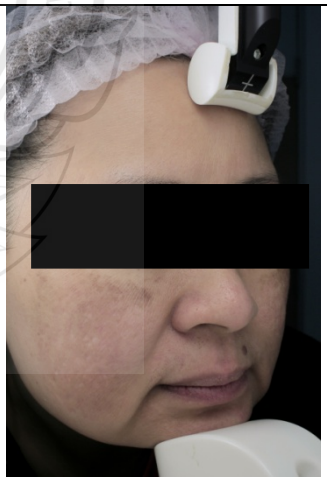
1	Before Treatment	End of Treatment
Left Side		
Central		
Right Side		

Figure A1 Before Treatment (Left) and End of Treatment (Right)

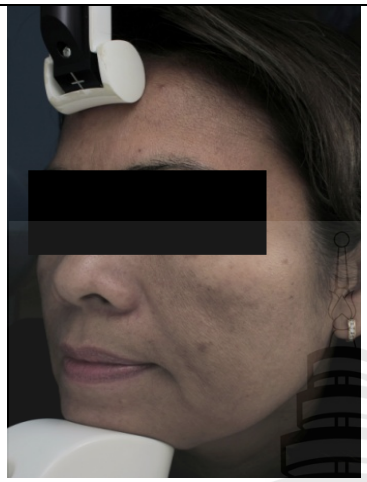
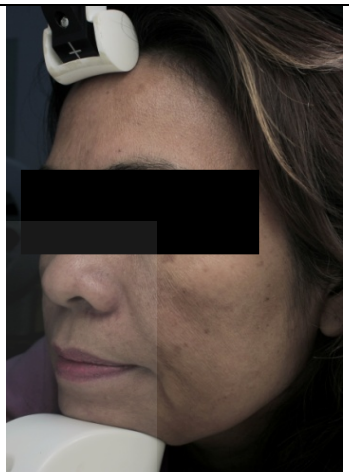
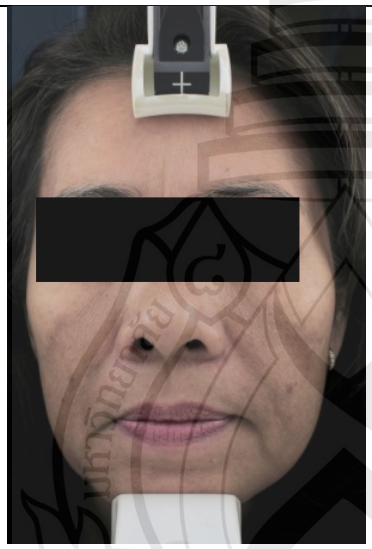
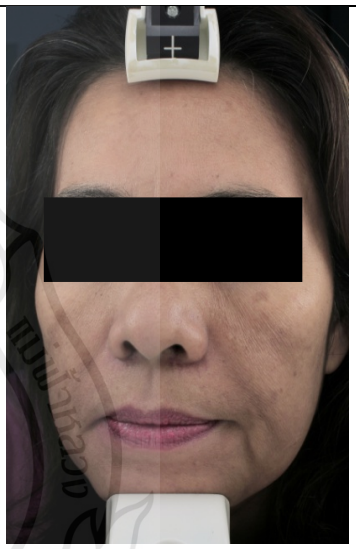
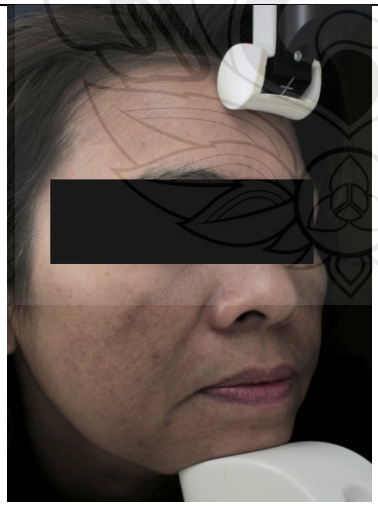
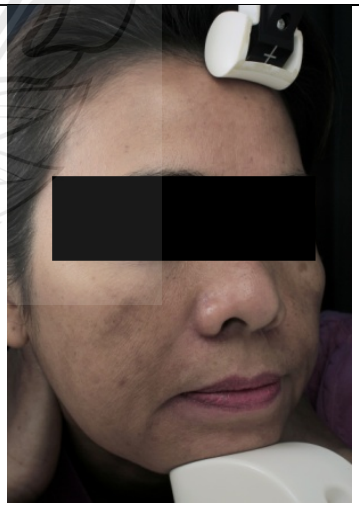
1	Before Treatment	End of Treatment
Sunflower Oil		
Placebo		
		

Figure A2 Before Treatment (Left) and End of Treatment (Right)

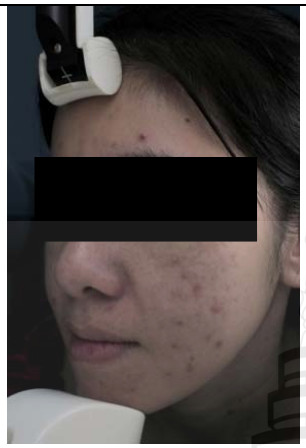
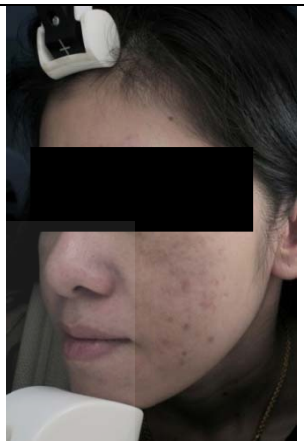
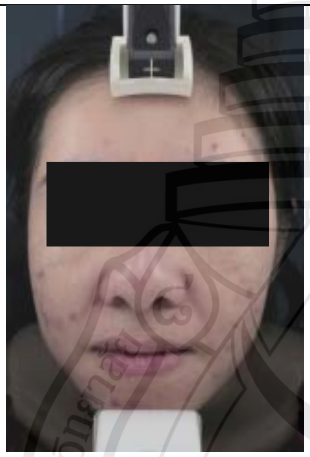
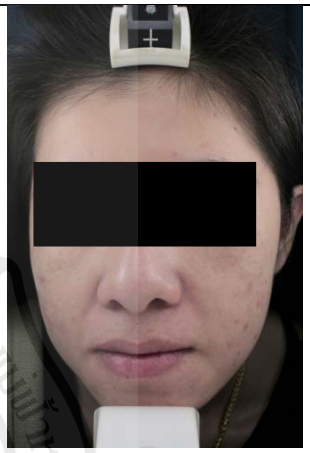
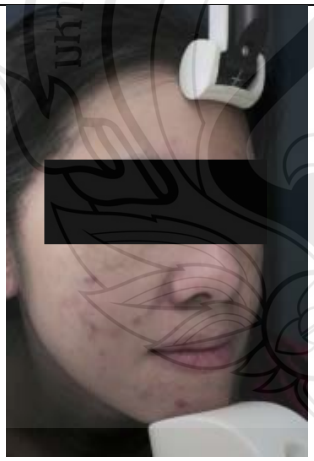
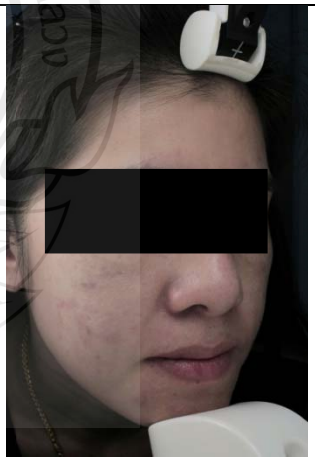
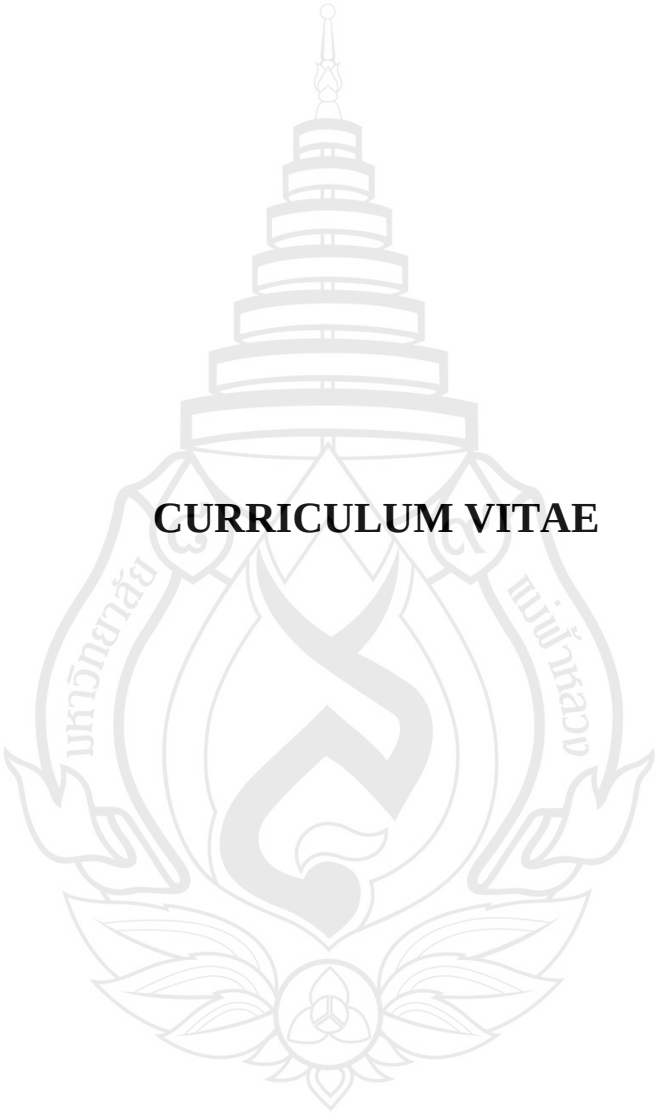
1	Before Treatment	End of Treatment
Lest Side		
Placebo		
		

Figure A3 Before Treatment (Left) and End of Treatment (Right)



CURRICULUM VITAE

CURRICULUM VITAE

NAME	Miss Nuttha Meesuntorn
DATE OF BIRTH	8 June1986
ADDRESS	1449/88 Bangsue, Bangkok, Thailand 10800

EDUCATIONAL BACKGROUND

2003-2009	Bachelor of Medicine Program (Doctor of Medicine, M.D.), Prince of Songkla University, Thailand.

WORK EXPERIENCE

2011	General Practitioner Doctor Chaiyo Hospital, Angthong
2010	Internist Doctor Angthong Hospital, Angthong