

## **PROTOCOL: Safety and Efficacy of Topical Agent, Oral Antioxidant, Laser Therapy and the Combination of Such for Melasma among Malaysians with Fitzpatrick Skin Type III-IV (STALCMA)**

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### **Introduction**

Melasma is a common acquired hyperpigmentation condition that mostly affects women of reproductive age, often occurring on the face area (Sarkar R et al., 2014). This chronic condition is often relapsing, causes great emotional suffering and has a detrimental impact on quality of life (Ikino JK et al., 2015). It is a condition that can only be managed but not cured completely (Sonthalia S et al., 2015). Melasma affects people of all ethnicities, however it occurs most commonly in Asian and Hispanic females (Fitzpatrick TB et al., 1987).

The incidence of melasma in South East Asia was 0.25% to 4% of patients seen in dermatology institutes, with peak incidence at age 30 to 44 years. A survey conducted at a dermatology clinic in Thailand found that the prevalence of melasma was as high as 40% in women and 20% in men. Melasma also accounted for 0.98% of cases reported in Indonesia and 4% of cases reported in Malaysia (Hann SK, 2007). The prevalence of melasma is high in South East Asia due to the tropical climate with high sun exposure. Moreover, lack of awareness amongst Asians on applying sunscreen also contributes to the development of melasma in the population.

There are a variety of treatment options available for melasma such as combination of topical agents such as hydroquinone and chemical peeling agents where it stops the transfer of melanin pigment produced onto the surface of the dermal layer by a specific transporter. Besides that, the presence of antioxidants such as tranexamic acid plays an important role in combating melasma where it stops the conversion of tyrosine. In clinic settings, the Q-switched Nd:YAG laser 1064nm with specific fluence is widely used as the main treatment for melasma. Furthermore, combination of this laser with topical agents and antioxidants are suggestive for good outcomes however with possible minimal to moderate side effects might happen (Rivas S et al., 2013).

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Although previously many studies have been done to evaluate the treatment of melasma using various approaches (Gheisari M et al., 2020; Kim HJ et al., 2017, Sim JH et al., 2014), there is limited study that has compared the efficacy and safety of oral and topical therapy versus physical therapy such as laser versus a combination of them for melasma. To be more precise, to-date, there is limited study that has evaluated the efficacy and safety of the treatment options for melasma such as topical hydroquinone, oral tranexamic acid, laser therapy and combination of them on Asian populations with Fitzpatrick skin type III-IV such as in Malaysia. Hence, this study aims to determine the efficacy and safety of these treatment options among Malaysian melasma patients with Fitzpatrick skin type III-IV. The findings of this study may help to establish the treatment options for clinical practice on melasma that suits Asian skin type III-IV.

### Research Questions

1. Is treatment with combination of topical hydroquinone 4% and oral antioxidant tranexamic acid 250mg bd for melasma among patients with Fitzpatrick skin type III-IV effective and safe?
2. Is treatment with Q-switched Nd:YAG (1064 nm) laser alone for melasma among patients with Fitzpatrick skin type III-IV effective and safe?
3. Is treatment with combination of Q-switched Nd:YAG (1064nm) laser with hydroquinone 4% and tranexamic acid 250mg bd among patients with Fitzpatrick skin type III-IV effective and safe?
4. Which is/are the best treatment modality in treating melasma in patients with Fitzpatrick skin type III-IV?
5. How satisfied are patients with the treatments they received for melasma?

### Underpinning theories

1. There is a significant different efficacy and safety on combination of topical hydroquinone

4%, oral antioxidant tranexamic acid 250mg bd and Q-switched Nd:YAG (1064nm) laser for melasma among patients with Fitzpatrick skin type III-IV versus other treatment options.

2. There is a significant different patients' satisfaction on combination of topical hydroquinone 4%, oral antioxidant tranexamic acid 250mg bd and Q-switched Nd:YAG (1064nm) laser for melasma among patients with Fitzpatrick skin type III-IV versus other treatment options.

### Methodology

Quasi experimental study design with simple random allocation using randomization tool application into 3 intervention arms which are: 1) topical hydroquinone 4% and oral antioxidant tranexamic acid 250mg bd or 2) Q-switched Nd:YAG (1064nm) laser therapy or 3) a combination therapy with all the triple treatment modalities in 1) and 2) (refer study flow chart). Patient recruitment and follow-up for intervention will be done at MAHSA Avenue Clinic, Petaling Jaya, Malaysia & UiTM. Patients will be enrolled into the study between July and December 2021.

Patient will be invited into the study if they fulfill the following inclusion and exclusion criteria.

#### Inclusion criteria:

- Malaysian adult aged 40-55 years old
- Fitzpatrick skin type III-IV
- Hyperpigmented lesion at face area determined by mMASI index

#### Exclusion criteria:

- Pregnant, lactating or patients with hormonal oral contraception
- Active cutaneous infection
- Use laser devices or similar treatments with depigmentation properties within the last 4 weeks

- Use of oral retinoid or other photosensitising drugs such as nonsteroidal anti-inflammatory drugs, tetracycline, phenytoin and carbamazepine
- Contraindications or known allergy or adverse event such as history of venous or arterial thromboembolic diseases or active thromboembolic diseases or chronic kidney disease patients to the treatment options.

The minimum sample size for the study is calculated based on resource equation approach for independent t-test. The calculation formula used is  $n = DF/k + 1$ ,  $n$ =sample size,  $DF$ =degree of freedom for the error,  $k$ =number of group. Hence 35 patients are required to be sampled for this study.

### Data collection process

Patients will be recruited into the study using internal invitation from the clinician and also through advertisement. Patients who are interested to participate will be brief about the study. Upon agreement they will be asked to sign the informed consent form to allow for their demographic, lifestyle and clinical data, imaging results and face photos to be used for research and publication purposes. Patients will be informed that their participation is voluntary and that they can withdraw from the study at any time without at risk to their other treatment or penalty. Patients will not receive any other incentive besides the treatments which will be provided to them at free-of-charge.

Patients will be selected into different treatment arms based on simple random allocation using randomization tool application. The treatment arms include patients who will received: 1) topical hydroquinone 4% and oral antioxidant tranexamic acid 250mg bd or 2) Q-switched Nd:YAG (1064nm) laser therapy or 3) a combination therapy with all the triple treatment modalities in 1) and 2) for 90 days. Follow-up will be done at 0, 30, 60 and 90 days.

For laser treatment, the intervention will be provided once a month. Demographic and lifestyle data such as age, gender, ethnicity, smoking status, average duration of sun exposure and clinical data for example Fitzpatrick skin type, health condition, medical, medication and allergy history, the modified Melasma Area and Severity Index (mMASI) score that has been validated (Pandya AG et al., 2011), image pigmentation score using JANUS-III and patient's satisfaction score will be collected at baseline and every follow-up accordingly. Patient recruitment will be done between 1<sup>st</sup> August to 31<sup>st</sup> October 2021. The minimum sample size for the study is calculated based on resource equation approach for independent t-test. The calculation formula used is  $n = DF/k + 1$ ,  $n$ =sample size,  $DF$ =degree of freedom for the error,  $k$ =number of groups (36) that is 12 patients for each treatment arm.

Topical hydroquinone 4% of Melashine® brand and oral antioxidant tranexamic acid 250mg bd of Transamine® brand will be used in this study. The patient will be instructed to use the topical agent at night everyday on the melasma skin area. For laser therapy, Q-switched Nd:YAG (1064nm) using Cosjet ATR® will be utilized.

### Data analysis

Data will be analysed descriptively and inferentially using Excel and SPSS (Version 27, IBM Corp, New York, NY). Demographic data will be presented as frequency, percentage, mean and standard deviation (SD) accordingly. Inferential analysis using ANOVA will be used to compare the image pigmentation score from JANUS-III, the score of mMASI and patient's satisfaction score between the groups, before and after intervention. A  $p$ -value of  $<0.05$  will be used as a statistically significant level. Imaging analysis from JANUS-III will be presented for comparison purposes before and after intervention.

## Ethics requirement & privacy

The ethical approval of this study will be obtained from MAHSA & UiTM Ethic Committee. The researchers will adhere to the principle of the Declaration of Helsinki and Malaysia Good Clinical Practice Guidelines. Only principal investigators and research teams have access to the data. Data management will be kept confidential in a protected computer and will be kept up to 2 years. Patient's personal information will be kept confidential and anonymous and presented collectively so that

nobody would be able to identify them individually.

## Expected survey output

The findings of this survey may help to establish the treatment options available for clinical practice guidelines on the treatment of melasma in Asian population with Fitzpatrick skin type III-IV. The data and report will be disseminated in the form of publications and presentations. The data set will be made available for the use of any interested party upon request.

## Study Flow Chart



## References

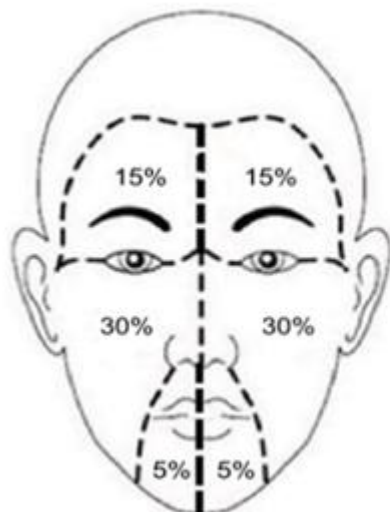
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**APPENDIX 1: MODIFIED MELASMA AREA AND SEVERITY INDEX (mMASI) SCORE**

Modified MASI score :

Modified MASI total score:	0.3 x A (Forehead) x D (Forehead) +
	0.3 x A (Left malar) x D (Left malar) +
	0.3 x A (Right malar) x D (right malar) +
	0.1 x A (Chin) x D (Chin)



**Table 1: Grading of the melasma area and severity index with its three parameters.**

<b>Area (A)</b>	0=No involvement; 1=<10% involvement; 2=11-29% involvement; 3=30-49% involvement; 4=50-69% involvement; 5=70-89% involvement; and 6=90-100% involvement.
<b>Darkness (D)</b>	0=normal skin color; 1=barely visible hyperpigmentation; 2=mild hyperpigmentation; 3=moderate hyperpigmentation; 4=severe hyperpigmentation.

**APPENDIX 2: Q-SWITCH LASER (TRIBEAM) TREATMENT PARAMETER**

<b>Pigmentation depth</b>	<b>Wavelength (nm) TH or G</b>	<b>Hand piece type</b>	<b>Spot size (mm)</b>	<b>Fluence</b>	<b>PTP</b>	<b>Immediate A/Event or E/Point</b>
Epidermal	532	Zoom	2-4	0.6-1.5	NA	Frosting
Dermal	1064TH		4-8	7.14.0	Off	Erythema