The Efficacy of Combination Topical Hydroquinone with Oral Tranexamic Acid, Q-Switched Laser Monotherapy and the Combination of Such in the treatment of Melasma Among Malaysian Males and Females with Fitzpatrick Skin Type III-IV

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Abstract

Melasma is a skin condition typically occurring in the Asian population amongst the middle-aged group. Hence, this study aimed to evaluate the efficacy of oral tranexamic acid and topical hydroquinone combination therapy, monotherapy with the 1064nm Q-switched Nd: YAG laser, and the combination of both therapies in treating melasma among Malaysian males and females with Fitzpatrick skin types III-IV. A quasi-experimental, unblinded study was done among 30 participants. Participants were divided into three groups and treated over three months. Group 1 received oral Tranexamic acid with 4% topical hydroquinone; Group 2 was treated with laser only, and Group 3 was treated with a combination of those three modalities. The researcher collected the modified Melasma Area and Severity Index (mMASI) score and image pigmentation score using the JANUS-III machine at each follow-up. The mean mMASI score was 4.80 ± 3.17 for Group 1, 4.96 ± 2.10 for Group 2, and 7.43 ± 4.15 for Group 3. Meanwhile, the mean UV spot for Group 1 was -1.22 ± 16.75, 2.09 ± 11.03 for Group 2 and -11.27 ± 5.83 for Group 3 respectively. The mean PL spots were 12.00 ± 12.073 for Group 1, 21.82 ± 10.19 for Group 2 and 9.36 ± 7.88 for Group 3. Both mean mMASI score and mean UV spot showed significant improvement after three months of treatment with a p-value < 0.05. However, the mean PL spot showed the most significant improvement with a p-value <0.05. The study found that 1064nm Q-switched Nd: YAG laser monotherapy is a better treatment in treating melasma among Malaysian with Fitzpatrick skin types III-IV.

Keywords: Melasma, oral tranexamic acid, topical Hydroquinone, Q-switched Nd: YAG laser

Melasma is a common hyperpigmentation condition that mainly affects women of reproductive age, commonly occurring on the face [1]. This chronic condition often relapses, causes great emotional suffering, and negatively impacts the quality of life [2]. It is a condition that can only be managed but not cured completely [1]. Melasma affects people of all ethnicities. However, it occurs most commonly in Asian and Hispanic females [3]. The incidence of melasma in Southeast Asia was 0.25% to 4% of patients seen in dermatology institutes, 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 was estimated to affect 0.98 percent of the population in Indonesia and 4 percent of the people in Malaysia [4]. The prevalence of melasma in Southeast Asia is high due to the tropical climate with high sun exposure. Furthermore, Asians' lack of understanding about applying sunscreen leads to the development of melasma in the population [5].

There are various treatment options available for melasma, such as a 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, antioxidants such as tranexamic acid play a vital role in combating melasma and stopping tyrosine conversion [6]. In clinic settings, the Q-switched Nd: YAG laser 1064 nm with specific fluence is widely used as the primary treatment for melasma [7]. Furthermore, combining this laser with topical agents and antioxidants is suggestive of good outcomes; however, possibly minimal to moderate side effects might happen [8].

Many studies have been done to evaluate the treatment of melasma using various approaches [9,10,11]. A survey by Nahla S. et al. showed that oral tranexamic acid and topical hydroquinone are more effective than hydroquinone alone in treating melasma [12]. Nevertheless, there is a scarcity of studies on the efficacy of dual Therapy of topical 4% hydroquinone and oral tranexamic acid versus Q-switched Nd: YAG laser monotherapy versus a combination of them for melasma. Moreover, study findings on these treatment options were even scarce among Asian populations with Fitzpatrick skin type III-IV, such as in Malaysia. Hence, this study aims to determine the efficacy of these treatment options: topical 4% hydroquinone and oral tranexamic acid, Q-switched Nd: YAG laser monotherapy, and the combination of such for the treatment of melasma among Malaysian males and females with Fitzpatrick skin type III-IV. This study's findings may help establish the best treatment option for melasma among Malaysian males and females with Fitzpatrick skin type III-IV.

Methodology

This study was conducted as a quasi-experimental, unblinded study. The participants were assigned systematically into three groups. Group 1 received oral antioxidant tranexamic acid 250 mg twice daily and topical hydroquinone at a 4 percent concentration. Group 2 received Q-switched Nd: YAG (1064 nm) laser monotherapy, and Group 3 received combination therapy using all available modalities. Participants were enrolled in the study from July till December 2021. Adult Malaysians between the ages of 40 and 55 who had hyperpigmented lesions according to the modified melasma area and severity index (mMASI) score on their faces and had Fitzpatrick skin types III-IV were eligible to participate in this study. An mMASI score was determined by two researchers who were the clinician treating the patients in this study. Patients were excluded from the study if they were pregnant or lactating, taking oral contraception, had an active skin infection, had used laser treatment or similar treatments with depigmentation properties within the last four weeks before the study, had used oral retinoid or

other photosensitizing drugs such as nonsteroidal anti-inflammatory drugs, tetracycline, phenytoin, and carbamazepine, had contraindications or known allergies or adverse event, venous or arterial thromboembolic diseases or active thromboembolic diseases or chronic kidney disease patients.

The required minimum sample size for the study was 35, as calculated based on the resource equation approach for the independent t-test[22]. The patients were briefed about the study. Upon agreement, they were asked to sign the informed consent form to allow their demographic, lifestyle, clinical data, imaging results, and face photos to be used for research and publication purposes. Patients were informed that their participation was voluntary and that they could withdraw from the study at any time without risk to their other treatment or penalty. Patients did not receive any additional incentive besides the treatments they provided at free-of-charge.

Follow-ups were done at 0, 30, 60, and 90 days. For the second treatment arm, laser treatments were provided once a month. Demographic and lifestyle data such as age, gender, ethnicity, smoking status, the average duration of sun exposure, and clinical data, for example, Fitzpatrick skin type, health condition, medical, medication, and allergy history, modified Melasma Area, and Severity Index (mMASI) score that had been validated [8], image pigmentation score using JANUS-III and patient's satisfaction score were collected at baseline and every follow-up accordingly. The modified MASI (mMASI) score, as the subjective assessment of the total area of involvement and darkness of melasma, is recognized as a reliable tool in the analysis of melasma [16]. The mean mMASI scores from all three treatment groups were assessed by comparing baseline reading (visit 1) and post-treatment (visit four). In the Janus-III system, three separate light sources are used with a high-resolution digital camera (normal, polarized (PL), and ultraviolet (UV) lights. It helps to evaluate the overall skin characteristic, including skin color, pores, sebum, porphyrin, and skin pigmentation. Various skin measurement devices have different measurement principles and algorithms for skin features. A previous study proved that the measured value of facial characteristics using the Janus-III system was highly associated with those made by a dermatologist [13]. They acquired the most accurate and similar data for pigmented areas since the measurement of the machine was based on high-resolution photographs, even with limited sample size [13].

Topical 4% hydroquinone of Melashine® and oral tranexamic acid 250mg bd (Transamine®) were used in treatment arm groups (1) and (3). The patients were instructed to use the topical agent every night on the melasma skin. Q-switched Nd: YAG (1064 nm) using Cosjet ATR® was utilized for laser therapy. Data were analyzed descriptively and inferentially using Excel and SPSS (Version 27, IBM Corp, New York, NY). Demographic data and patient satisfaction scores were presented as frequency, percentage, mean and standard deviation (SD). Inferential analysis was done using ANOVA to compare the pigmentation mMASI score and imaging analysis from JANUS-III, which is the UV spot and PL spot between the three groups. The before and after intervention score was compared using paired t-test. A p-value of <0.05 was considered a statistically significant level. The ethical approval of this study was obtained from MAHSA University Ethic Committee (RMC/EC56/2021). The researchers adhered to the principle of the Declaration of Helsinki and Malaysia Good Clinical Practice Guidelines. Only the principal investigator and research team members have access to the data. Data management was kept confidential on a protected computer for up to 2 years. Patients' personal information was kept confidential and anonymous and presented collectively so that

nobody would be able to identify them individually.

Results

A total of 30 participants were included in the study with nine participants in Group 1, 11 participants in Group 2, and 10 in Group 3. The mean age and standard deviation (SD) of patients in Groups 1, 2, and 3 were 50.44 ± 9.07, 49.82 ± 7.48 and 47.91 ± 7.30, respectively. In the study, female and Malay patients predominate in all three groups. The average sun exposure was reported to be higher in Group 2 with a mean of 4.36 ± 3.17, followed by Group 3 with 3.09 ±2.63 and Group 1 with 2.78 ± 3.38 to be the lowest. Amongst all groups, Group 2 has the highest frequency of sunscreen usage with a mean of 2.18 ± 1.54. The mMASI baseline score was highest in Group 3 with the mean of 7.43 ± 4.15, followed by 4.96 ± 2.10 in Group 2 and 4.80 ± 3.17 in Group 1. The mean for the UV Spot baseline shows the highest score referring to improvement in Group 3 which was -11.27 ±5.83 followed by Group 1 which was -1.22 ±6.75 and Group 3 which was 2.09 ± 11.03. One way ANOVA test revealed that there were significant differences in PL spot baseline, F (2,28) = 4.64, p-value = 0.02, and UV spot baseline, F (2,28) = 3.88, p-value = 0.03, across the three groups. The post hoc test revealed a significant difference in PL spot baseline between group 2 (21.82 ± 10.19) and group 3 (9.36 ± 7.88). Similarly, for the UV spot baseline, there was a significant difference between group 2 (2.09 ± 11.03) and group 3 (-11.27 ± 5.83).

The pre and post treatments effectiveness were compared and analyzed for all three groups. All the treatment plan groups showed significant improvement in mMASI score with a p-value of < 0.05. The largest mean difference (Standard Error, SE) in mMASI score pre- and post-intervention was seen in Group 3 with the value of -6.72 (SE = 3.36), followed by Group 1 with a mean difference of -5.23 (SE = 2.61) and Group 2 with a mean difference of -3.55 and SE of 1.78. Regarding the UV spot outcomes, only Group 2 significantly improved melasma condition pre-post intervention with a mean difference of 16.63 and SE of 8.31 (p = 0.005). When mean PL spot outcomes were evaluated, a similar pattern was found. Only Group 2 had significant improvement pre- and post-intervention (p = 0.001) with a mean difference of 19.13 and SE of 9.56. Groups 1 and 3 did not report a significant improvement in mean UV spot and mean PL spot outcomes pre- and post-intervention. Table 2 summarizes pre-post melasma treatment efficacy for the different treatment types.

When treatment outcomes in each visit were evaluated, all measured outcomes reported a significant difference within groups (p < 0.05). However, only the mMASI score showed a significant difference between the groups (p < 0.005). In Group 1, the mean difference of mMASI score during the second visit was -2.22 (SE = 1.1), and this was further reduced in visit 3 with a mean of -0.47 (SE = 0.24). However, the score was increased in visit 4 with a mean of 1.24 (SE = 0.62). In Group 2, where patients received laser treatment as monotherapy, there was a continuous reduction in the mean difference mMASI scores from visits 2 to 4, which were -2.43 (SE = 1.22), -1.1 (SE = 0.55), and -0.02 (SE = 0.01). Among patients receiving combination treatment for Group 3, the mean difference of mMASI score at visit two was -3.12 (SE = 1.56), followed by -1.02 (SE = 0.51) in visit 3 to -2.58 (SE = 1.29) in visit 4.

For the PL spot outcomes, the mean difference in Group 1 between visit 2 and 1 was -2.6 (SE = 1.3), visit 3 and 2 of -0.8 (SE = 0.4), and a marked increase in score in the final visit with a mean difference of 3.4 (SE=1.7). for the laser treatment group, Group 2, the mean difference of PL spot during visits 2 to 1 was -2.75 (SE = 1.38). The result was further improved in visits3 and 4 with mean differences of -1.13 (SE = 0.57) and -15.5 (SE = 7.63), respectively. In Group 3, the mean difference in

Table 1: Sociodemographic Comparisons for monotherapy, dual therapy and triple Therapy of participants (n=30)

Variables	Topical Hydroquinone + Oral Tranexamic Acid Dual Therapy (n=9) (n (%), Mean ± SD)	Q-switched Nd: YAG Laser Monotherapy (n 11) (n (%), Mean ± SD)	Topical Hydroquinone + Oral Tranexamic Acid + Q-switched Nd: YAG Laser Triple Therapy (n=10) (n %, Mean ± SD)	p-value
Age	50.44 ± 9.07	47.91 ± 7.30	49.82 ± 7.48	0.75
Gender				0.39
Male	0 (0)	0 (0)	1 (9.1)	
Female	9 (100)	11 (100)	10 (90.9)	
Ethnicity				0.39
Malay	6 (66.7)	10 (90.9)	8 (72.7)	
Chinese	0 (0)	0 (0)	0 (0)	
Indian	3 (33.3)	1 (9.1)	3 (37.3)	
Others	0 (0)	0 (0)	0 (0)	
Average sun exposure (hours)	2.78 ± 3.38	4.36 ± 3.17	3.09 ± 2.63	0.47
Frequency of sunscreen usage	1.00 ± 0.87	2.18 ± 1.54	1.64 ± 1.12	0.12
mMASI baseline	4.80 ± 3.17	4.96 ± 2.10	7.43 ± 4.15	0.13
PL Spot Baseline	12.00 ± 12.073	21.82 ± 10.19*	9.36 ± 7.88*	0.02*
UV Spot Baseline	-1.22 ± 16.75	2.09 ± 11.03*	-11.27 ± 5.83*	0.03*

*Significant at 0.05

PL spot outcomes in visits 2 to 1 was 3.33 (SE = 1.67), -2.33 (SE = 1.17) for visits 3 to 2, and a slight increment in score in visits 4 to 3 with a mean difference of -3.67 (SE = 1.84).

As for the UV spot outcomes, the mean difference of score for Group 1 between visits 2 to 1 was -3.6 (SE = 1.8), 3.2 (SE = 1.8) for visits 3 to 2, and subsequently reduced slightly in the visit 4 to 3 with a mean of 0.6 (SE = 0.3). In Group 2, during visits 3 to 2 with a mean of 0.88 (SE=0.44) and the markedly increased during visit 4 to 3 with a mean of 17.13 (SE=9.07). In Group 3, mean difference of the UV spot score between visits 2 to 1 was -13.93 (SE = 3.67), with a marked reduction in visits 3 to 2 with a mean difference score of -0.5 (SE = 0.44). The score was further increased in visit 4 with a mean difference of 2.17 (SE = 1.09).

Table 3 summarizes the mean differences of mMASI, UV PL spots and UV spot outcomes for each intervention visit for the three treatment

Table 2:The mean difference of participants' mMASI, PL spots, and UV spots among three treatment regimens (n=30)

Treatment Regimen	Topical Hydroquinone + Oral Tranexamic Acid Dual Therapy (n=9)		p-value	Q-switched Nd:YAG Laser Monotherapy (n=11)		p-value	Topical hydroquinone + Oral Tranexamic Acid + Q-switched Nd: YAG Laser Triple Therapy (n=10)		p-value
	Pre	Post		Pre	Post		Pre	Post	
Mean mMASI	4.57 ± 3.60	-0.66 ± 0.49	0.02*	4.61 ± 0.72	1.06 ± 0.72	0.01*	8.47 ± 4.65	1.75 ± 0.74	0.01*
Mean UV Spot	3.20 ± 14.36	2.20 ± 17.33	0.88	1.00 ± 10.80	17.63 ± 16.71	0.01*	-13.33 ± 6.65	-4.33 ± 21.23	0.24
Mean PL Spot	14.20 ± 7.19	14.20 ± 10.31	1.00	22.13 ± 10.80	3.00 ± 12.31	0.00*	9.17 ± 8.18	6.50 ± 8.67	0.27

modalities.

Discussion

Melasma is a chronic skin problem commonly happening among Asian women. Although there are numerous melasma treatment options, there is no "gold standard", which presents a dilemma for aestheticians and dermatologists. In this study, a total of 30 patients were recruited to the three treatment arms, with the majority of the patients included being female. This could be because the melasma problem was reported to be more common among females than males [14]. Malays and Indians have a higher number seeking treatment related to melasma in this study because they tend to have darker skin color, which has a higher risk of developing skin pigmentation problems than Chinese and others [24]. Since the patients were assigned to follow their specific treatment modalities, blinding was impossible to be done in this study.

Hydroquinone, tranexamic acid and Q-switched Nd: YAG laser were three treatment modalities used in this study. Hydroquinone (used in treatment arms 1 and 3) is the most popular depigmenting agent used worldwide in treating melasma, especially of the epidermal [23]. Tranexamic acid (used in treatment arms 1 and 3) is the first systemic Therapy that has demonstrated efficacy for melasma in Asian skin over a short duration of treatment (8–12 weeks) besides its other advantages, such as being easy to administer and safe with few, reversible, mild side effects [12]. While Q-switched Nd: YAG laser (used in treatment arms 2 and 3) has been the most effective among Qs lasers, especially with the use of sub photo thermolytic fluencies to reduce side effects for the treatment of melasma [15]. A randomized, controlled, double-blind study has suggested that oral tranexamic acid in combination with topical hydroquinone significantly improves melasma [16].

Table 3: The mean difference of mMASI, PL, and UV spot for each visit (n=30)

	Topical Hydroquinone + Oral Tranexamic Acid Dual Therapy		Q-switched Nd: YAG Laser Monotherapy		Topical hydroquinone + Oral Tranexamic Acid + Q-switched Nd: YAG Laser Triple Therapy		Between Group F (*p*)	Within Group F (*p*)	Interaction (*p*)
	Mean difference	SE	Mean difference	SE	Mean difference	SE			
mMASI							4.65 (0.02)	32.27 (<0.001) *	1.55 (0.023) *
Visit 2 -1	-2.22	1.10	-2.43	1.22	-3.12	1.56			
Visit 3-2	-0.47	0.24	-1.11	0.55	-1.02	0.51			
Visit 4-3	-1.24	0.62	-0.02	0.01	-2.58	1.29			
PL Spot							0.77 (0.48)	9.71 (0.001) *	8.20 (<0.001) *
Visit 2-1	-2.6	1.3	-2.75	1.38	3.33	1.67			
Visit 3-2	-0.8	0.4	-1.13	0.57	-2.33	1.17			
Visit 4-3	3.4	1.7	-15.5	7.63	-3.67	1.84			
UV Spot							1.63 (0.23)	5.11 (0.01) *	3.45 (0.02) *
Visit 2-1	-3.6	1.8	-0.62	0.31	-13.93	3.67			
Visit 3-2	3.2	1.6	-0.88	0.44	-0.5	0.44			
Visit 4-3	-0.6	0.3	17.13	9.07	2.17	1.09			

This study noted that the mean mMASI, mean UV spot, and mean PL spot showed the most significant improvement with a p-value of <0.005, <0.005, and <0.001, respectively. After three months of total study duration, there was a significant difference within groups ($p < 0.05$); however, only the mMASI score shows a significant difference between the groups ($p < 0.005$). Noted in the oral treatment group, there was an increase in the mean PL spot during the 4th visit, which was due to non-adherence to the sunscreen, as stated by the respondents after further questioning. Otherwise, the mean for the mMASI and UV spot showed a better outcome. This study showed that Q-switched Nd: YAG laser significantly reduced the mean mMASI score among melasma patients (p=0.005). Other therapies did not improve mean mMASI scores among melasma patients. This finding was similar to a previous study that showed a significant reduction in mean mMASI score after treatment with a Q-switched Nd: YAG laser [17].

The resulting data showed that only Q-switched Nd:YAG laser monotherapy significantly reduced the mean UV spot score (p=0.005) and the PL spot score (p=0.005).

From our data, the Q-switched Nd: YAG laser monotherapy had shown a greater efficacy for treating melasma than the combination of topical 4% hydroquinone and oral antioxidant tranexamic acid dual therapy and the combination therapy with all triple treatment modalities. This contradicted a previous study suggesting that combining topical hydroquinone and oral tranexamic acid dual therapy was associated with more significant improvement than oral tranexamic acid combined with Q-switched Nd: YAG laser dual therapy [18]. However, the study did not evaluate the effect of triple Therapy. Our finding was also contradicted by a systematic review by Neagu et al. that showed that combination treatments (combining oral treatment, micro needling, chemical peelings, topical creams, or lasers) had been proved to be the best solution, either in double or triple combinations [19]. A reason to explain this contradiction was due to our study location. Malaysia is located near the equator line since sunlight strikes the Earth most directly at the equator, UV strength~~,~~ at its highest intensity level. When combined with the possibility that the patients in Group 3 who received the triple Therapy developed dehydrated skin compared to the rest, this location factor explained the slower progress of melasma treatment in Group 3 patients.

Our finding was similar to a previous study by Vachimaron et al. that studied the efficacy of laser alone compared to a combination of laser and glycolic acid peels. They reported temporary improvement on both sides, but the side effects, such as post-inflammatory hyperpigmentation, were more common on the side treated with a combination protocol [20]. The strength of our study was its quasi-experimental design that mimicked an experiment, provided a high level of evidence, and was less expensive. Our study evaluated the real-world efficacy of an intervention implemented by clinicians rather than the effectiveness of an intervention implemented by research staff under research conditions. Another strength of this study was that we used two types of melasma assessment tools: subjective-based, referring to the mMASI score, and objective-based, referring to the Janus-III system. By having these two assessment tools, the results were more reliable as another captured the skin conditions that were not captured by one assessment tool.

While conducting this study, we encountered various limitations. Because the study was conducted during the pandemic of covid-19, we could not acquire a significant sample size. As a result, we could not gather all the participants in one location and had to locate some of them in separate locations. For various reasons, some of our patients failed to follow up during subsequent sessions. Conflict arose in the first group when the patients opted not to come because there was concern about taking the oral

drug for three months after reading about the misconception risks on the internet. The patients' compliance with everyday skincare routines, such as sunscreen usage at home, was one element we could not avoid. Aside from that, we also had no control over the patient's working environment; due to the difference in the working environment, some of them may be exposed to the sunlight for more than 5 hours a day which potentially disturbed the progress of existing pigment disruption. Further research needs to be done to study the rate of recurrence and rebound of melasma after all three treatments. There is also a need for another study using larger sample size.

Conclusion

The Q-switched Nd: YAG laser monotherapy is superior to the combination of topical 4% hydroquinone and oral antioxidant tranexamic acid dual therapy and the combination therapy with all triple treatment modalities in the treatment of melasma in patients with Fitzpatrick skin type III-IV. Thus, we suggest that the Q-switched Nd: YAG laser monotherapy should be considered the first treatment option in treating melasma in this population.

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Conflict Of Interest

There is no conflict of interest reported in this study.

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