Topical Isotretinoin for Melasma in Thai Patients: A Vehicle-Controlled Clinical Trial

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Abstract

Background: Melasma is an acquired hyperpigmentary disorder commonly seen in Orientals. Recently it has been demonstrated that tretinoin (all-trans-retinoic acid) can produce significant clinical improvement of melasma. However, moderate cutaneous side effects (retinoid dermatitis) occurred in a number of patients.

Objective: To investigate the efficacy of topical 0.05 per cent isotretinoin gel (Isotrex) in the treatment of melasma in Thai patients.

Method: Thirty patients with moderate to severe melasma entered a 40-week, randomized, vehicle-controlled clinical trial in which they applied either 0.05 per cent isotretinoin gel, or its vehicle base together with a broad spectrum sunscreen (SPF 28) daily to the entire face. They were evaluated clinically (using Melasma Area and Severity Index), and colorimetrically (using our Melasma Area and Melanin Index).

Results: After 40 weeks, the average MASI and MAMI scores of the isotretinoin-treated group decreased by 68.2 per cent and 47 per cent respectively, while the corresponding control scores declined 60 per cent and 34 per cent. There was no statistically significant difference between the isotretinoin and vehicle groups. When the MASI and MAMI scores of each visit were compared to their baseline data, a statistically significant reduction of the score was first noted at weeks 4 and 12 respectively. Lightening of melasma, as determined clinically (MASI score), correlated well with pigmentation measurements (MAMI score). Side effects were limited to a mild transient "retinoid dermatitis" occurring in 27 per cent of isotretinoin-treated patients.

Conclusion: Daily use of broad spectrum sunscreen has a significant lightening effect on melasma in Thai patients. However, there was no statistically significant difference between the isotretinoin and vehicle-treated group.

Key word : Melasma, Treatment, Isotretinoin

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Melasma is an acquired masklike, facial hyperpigmentation. The pathogenesis of melasma in Orientals is not fully understood, but pregnancy, estrogen ingestion, UV light exposure, and family history are well-recognized associations in Caucasians[1]. Although melasma is seen in both sexes and all races, women are most commonly affected, and it appears to be more prevalent in darkly pigmented races[1-3]. Hydroquinone is probably the most widely used drug, which has been used alone and in combination with corticosteroids or retinoic acid[4,5]. The use of hydroquinone is inadvisable because of the risk of depigmentation, dermatitis and ochronosis,[2,6] and topical corticosteroids may produce skin atrophy and telangiectasia. Recently it has been shown that, as monotherapy, tretinoin (all-trans-retinoic acid) can produce significant clinical improvement of melasma, but the improvement is rather slow[7,8]. Moreover, treatment with tretinoin is associated with local irritation (retinoid dermatitis) in many patients,[7,8] a factor that may limit its therapeutic usefulness.

We have attempted to identify another retinoids that may have improved therapeutic profile for the treatment of melasma. Because isotretinoin resembles tretinoin chemical structure, and has many similar therapeutic effects on many skin diseases such as acne vulgaris[9], and photoaging [10], we considered it worthwhile to try this well-tolerated treatment modality on melasma. We conducted a vehicle-controlled investigation to assess the efficacy of topical 0.05 per cent isotretinoin gel in the treatment of melasma in Thai patients. Study participants were also assessed for type and distribution of melasma.

MATERIAL AND METHOD

Patients

Thirty Thai patients (26 female, 4 male) with moderate to severe facial hypermelanosis clinically consistent with melasma entered the 40-week study. Fifteen patients were treated with isotretinoin gel and 15 with its vehicle base. Prior to entry in the study, patients had to cease using systemic retinoids for 6 months or topical retinoids for 1 month. None of the patients had used topical steroid creams or other agents on their face for at least 2 weeks prior to the study. Women of childbearing age were to use an approved method of contraception, and pregnant or nursing women were excluded. The subjects were asked not to expose themselves to ambient sunlight during the study. All patients signed informed consent forms, and the protocol was approved by the institutional review board of Mahidol University.

Study design

Patients were randomly assigned to either isotretinoin or vehicle treatment, on the basis of a computer-generated randomization code. Isotretinoin 0.05 per cent gel (Isotrex) and its color-matched vehicle, were supplied by Stiefel Laboratories Ltd. Neither investigator nor patient was aware of group assignment.

Treatment

Study patients were instructed to initially apply a "pea-sized" amount of test cream to their entire face (to treat clinically inapparent as well as apparent melasma) twice daily. They were directed to slowly increase the amount used to tolerance. A broad spectrum sunscreen with a sun-protection factor of 28 (Butyl methoxydibenzoylmethane 2%, padimate O 8%, oxybenzone 3%, titanium dioxide 2%) was supplied to all patients to be used daily and before exposure to sunlight. Use of emollients was encouraged.

Clinical evaluations

Patients underwent clinical evaluations by a single physician throughout the 40-week study. Evaluations were undertaken at baseline, after 2 and 4 weeks of therapy, and at monthly intervals until study termination at 40 weeks. No makeup was worn by patients at any clinical assessment or photographic session.

At the baseline visit, history of melasma regarding length of time present, relationship to pregnancy, hormonal therapy, sun exposure, and cosmetic use was taken. Patients were asked about previous use of hydroquinones and family history of melasma. A clinical type of melasma by pattern was assigned to each patient as centrofacial, mandibular, or malar. Wood's light was used to determine melasma type as epidermal, dermal, or mixed. Mixed and indeterminant types were considered equivalent for purposes of this study.

Clinical evaluations of skin color were made at each visit. For more accurate quantification of the severity of melasma and its changes during therapy, a Melasma Area and Severity Index (MASI) score as proposed by Kimbrough-Green et al[8].

Table 1. Grading of Melasma Area and Severity Index (MASI).

	Factor	Area (A)	Severity of melasma
Forehead (F)	0.3	A_F	D_F+H_F
Right Malar (MR)	0.3	A_{MR}	$D_{MR}+H_{MR}$
Left Malar (MF)	0.3	A_{MF}	$D_{MF}+H_{MF}$
Chin (C)	0.1	A_C	D_C+H_C

A = Area involvement: 0=0%; 1=10%; 2=10-29%; 3=30-49%; 4=50-69%; 5=70-89%; 6=90-100%
D = Darkness: 0=absent; 1=slight; 2=mild; 3=marked; 4=severe
H = Homogeneity 0=minimal; 1=slight; 2=mild; 3=marked; 4=severe

$MASI = 0.3(D_F+H_F)A_F + 0.3(D_{MR}+H_{MR})A_{MR} + 0.3(D_{MF} + H_{MF})A_{MF} + 0.1\ (D_C+H_C)A_C$

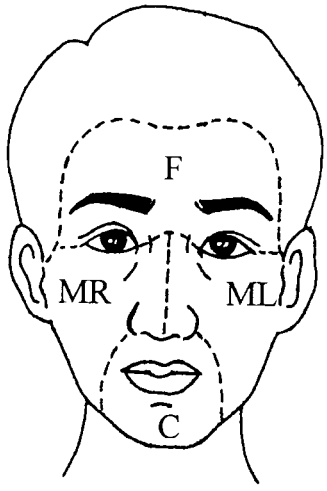

Fig. 1. Areas of the face using in the calculation of the Melasma Area and Severity Index (MASI) and the Melasma Area and Melanin Index (MAMI): forehead (F), right malar area (MR), left malar region (ML), and chin (C).

(Table 1) was devised and calculated for each subject at baseline and at each visit. This calculation was based on a scoring system similar to that devised for psoriasis[11]. Four areas of the face were evaluated for use in the calculation: forehead (F), right malar area (MR), left malar region (ML), and chin (C), corresponding to 30 per cent, 30 per cent, 30 per cent, and 10 per cent of the total face, respectively (Fig. 1). The melasma in each of these four areas (A_F, A_{MR}, A_{ML}, and A_C) was given a numerical value: 0, no involvement; 1, less than 10 per cent; 2, 10 per cent through 29 per cent; 3, 30 per cent through 49 per cent; 4, 50 per cent through 69 per cent; 5, 70 per cent through 89 per cent; and 6, 90 per cent through 100 per cent. Severity of melasma was based on two factors: darkness (D) of melasma compared with normal skin and homogeneity (H) of hyperpigmentation. These were assessed according to a scale of 0 to 4 in which 0 means minimal homogeneity or absence of darkness and 4 represents the most severe possible manifestation (Table 1). To calculate the MASI score, the sum of the severity rating for darkness (D) and homogeneity (H) was multiplied by the numerical value of the areas involved (A) and by the various percentages of the four facial areas. These values were added to obtain the MASI score. The formula can be written as:

$MASI = 0.3(D_F+H_F)A_F + 0.3(D_{MR}+H_{MR})A_{MR} + 0.3(D_{MF} + H_{MF})A_{MF} + 0.1\ (D_C+H_C)A_C$

Skin color measurement and Melasma Area and Melanin Index (MAMI)

The melasma color at each involved site (forehead, right malar, left malar, and chin) were measured at baseline and at each visit with a reflectance spectrophotometer (Dermaspectrometer, Cortex Technology, Denmark)[12], where each measure consisted of 5 averaged measurements of each target area. This instrument irradiates the skin with a known intensity of red (655 nm) and green light (568 nm) and measures the reflexion, which gives an erythema index (EI) and melanin index (MI) related to the erythema and pigmentation of the skin. Equations for calculation of erythema-index and melanin-index are built into the instrument. One measurement takes about 10 seconds.

Table 2. Grading of Melasma Area and Melanin Index (MAMI).

	Factor	Area (A)	Melanin Index (MI)
Forehead (F)	0.3	A_F	MI_F
Right Malar (MR)	0.3	A_{MR}	MI_{MR}
Left Malar (MF)	0.3	A_{MF}	MI_{MF}
Chin (C)	0.1	A_C	MI_C

A = Area involvement: 0=0%; 1=10%; 2=10-29%; 3=30-49%; 4=50-69%; 5=70-89%; 6=90-100%

$MAMI = 0.3*MI_F*A_F + 0.3*MI_{MR}*A_{MR} + 0.3*MI_{MF}*A_{MF} + 0.1*MI_C*A_C$

For more accurate quantification of the severity of melasma and any change during therapy, a Melasma Area and Melanin Index (MAMI) score was devised and calculated for each subject at baseline and at each visit. This calculation was based on a scoring system similar to that devised for MASI score. However, the severity of melasma was based on a melanin index (MI) instead of darkness (D) and homogeneity (H) of melasma. To calculate the MAMI score, the melanin index (MI) was multiplied by the numerical value of the areas involved (A) and by the various percentages of the four facial areas. These values were added to obtain the MAMI score (Table 2). The formula can be written as:

$$MAMI = 0.3*MI_F*A_F + 0.3*MI_{MR}*A_{MR} + 0.3*MI_{MF}*A_{MF} + 0.1*MI_C*A_C$$

Tolerability and efficacy

At each visit tolerability was determined by localized erythema, peeling, burning sensation, or pruritus in the treatment area. These factors were assessed on a four-point scale as absent, mild, moderate, or severe.

Photography

Color photographs of patients were taken by a professional photographer at baseline and after 3, 6 and 10 months of therapy. En face, left and right poses were used for all patients. During subsequent photographic sessions, each patient's baseline photographs were examined by the photographer to verify that the current orientation matched baseline.

Statistical Method

Changes in clinical (MASI score) and skin color (MAMI score) parameters of melasma between isotretinoin- and vehicle-treated groups were compared using a two-sample *t* test. The strength of the relationship between the MASI and MAMI values was assessed with simple linear regression model. The MASI and MAMI scores of each visit were compared to their baseline data using a paired *t*-test. All P values were two sided. Summary statistics were expressed as mean ± SE.

RESULTS

Twenty-three patients completed 40 weeks of treatment (11 patients in the isotretinoin group and 12 patients in the vehicle group). Of the seven patients who dropped out of the study, 4 had been assigned to the isotretinoin group and 3 to the vehicle group. Two patients (one in the isotretinoin group and one in the vehicle group) dropped out at weeks 20, another two patients (one in the isotretinoin group and one in the vehicle group) dropped out at weeks 36, the last 3 patients (two in the isotretinoin group and one in the vehicle group) dropped out in the last week. The reasons for dropping out were: non-compliance (3 isotretinoin, 3 vehicle) and pregnancy (one isotretinoin).

Patient Demographics

The average age for the isotretinoin group was 38 years, and for vehicle group was 40 years. Prior to study entry, 5 patients had used hydroquinone without benefit. For patient demographics see Table 3.

Melasma Area and Severity Index (MASI)

After 40 weeks, the average MASI score of the isotretinoin-treated group decreased by 68.2 per cent from 8.57 ± 1.7 at baseline to 2.73 ± 1.2, compared with a 60 per cent decrease, from 8.93 ± 5 to 3.6 ± 0.9, in the vehicle group (p=0.4337, Fig. 2).

Table 3. Patient demographics.

Variable	0.05% Isotretinoin gel (n=15)	Vehicle (n=15)	Overall (n=30)
Sex, M/F	3/12	1/14	4/26
Age, y*	38 ± 10	40 ± 10	39 ± 10
Age at onset, y*	27 ± 3.1	32 ± 10.4	30 ± 8.1
Duration of melasma, y*	9 ± 5.5	5 ± 3.3	7 ± 5
Baseline MASI score*	8.57 ± 6.6	8.93 ± 5	8.75 ± 5.8
Baseline MAMI score*	87 ± 45	94 ± 47	91 ± 45
Distribution of melasma, No. (%)			
Centrofacial	6 (40)	8 (53)	14 (47)
Mandibular	2 (13)	1 (7)	3 (10)
Malar	7 (47)	6 (40)	13 (43)
Type of melasma by Wood's light, No. (%)			
Epidermal	1 (7)	1 (7)	2 (7)
Dermal	2 (13)	0 (0)	2 (7)
Mixed	12 (80)	14 (93)	26 (87)
Family history, No. (%)	10 (67)	6 (40)	16 (53)

* Values are expressed as mean ± SD
MASI indicates Melasma Area and Severity Index
MAMI indicates Melasma Area and Melanin Index

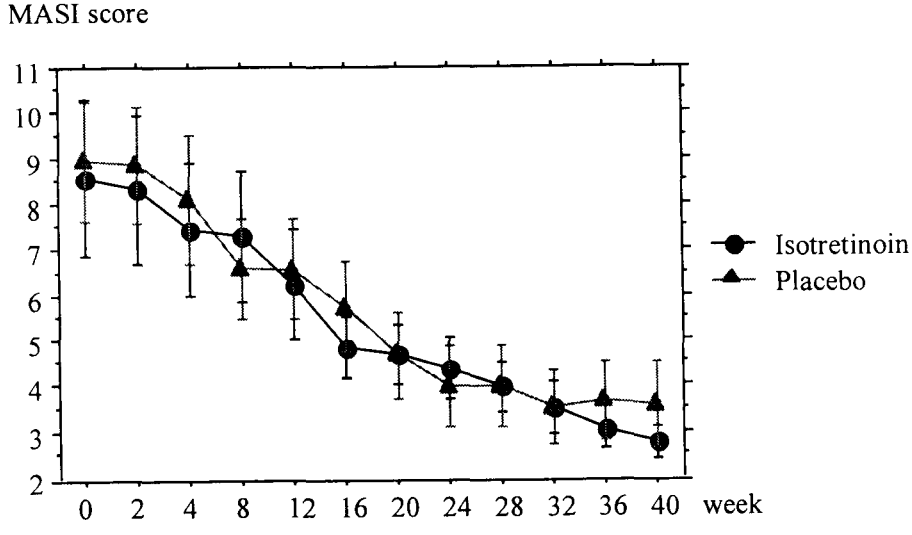

Fig. 2. Change in MASI score after treatment with 0.05 per cent isotretinoin gel or vehicle. Values are expressed as mean ± SE of MASI score.

When the MASI scores of each visit were compared to their baseline data, a statistically significant reduction of the score was noted at week 4 and thereafter in both isotretinoin- and vehicle-treated groups ($p<0.02$, Fig. 2).

Melasma Area and Melanin Index (MAMI)

The reductions of MAMI score after 40-weeks treatment with isotretinoin gel and vehicle were 47 per cent and 34 per cent respectively. When the mean between the MAMI score of the 2

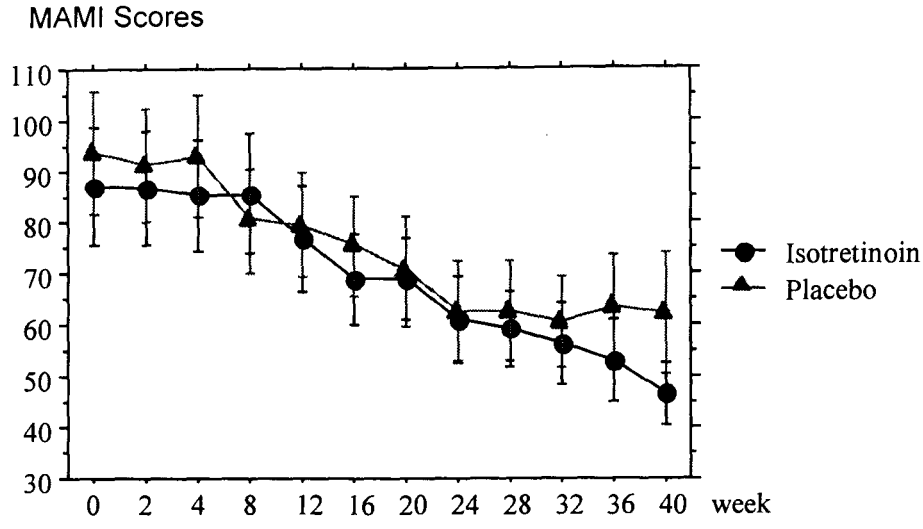

Fig. 3. Change in MAMI score after treatment with 0.05 per cent isotretinoin gel or vehicle. Values are expressed as mean ± SE of MAMI score.

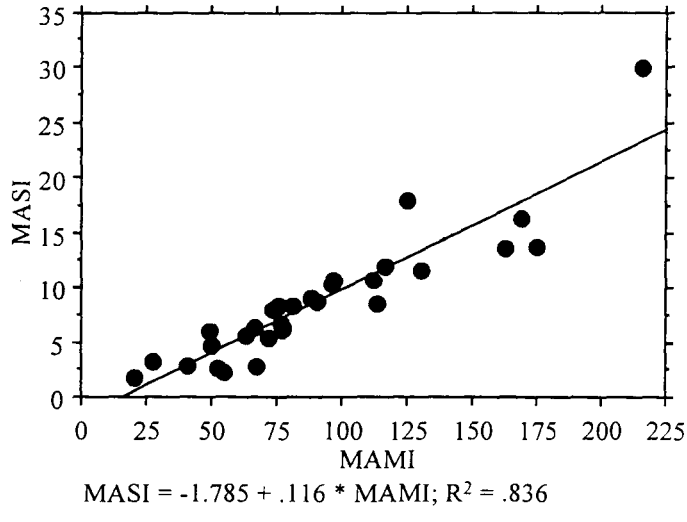

Fig. 4. Relation between MASI and MAMI score at the baseline in 30 patients (r^2=0.836, p=0.0001). The line represents the best linear fit as determined by the least-squares method.

groups was analyzed using the paired *t*-test, no statistically significant difference was found (p = 0.2587, Fig. 3).

When the MAMI scores of each visit were compared to their baseline data, a statistically significant reduction of the score was first noted at week 12 in both isotretinoin- and vehicle-treated groups (p<0.02, Fig. 2).

Relationship between MASI and MAMI score

The relation between the MASI and MAMI score is very good, as shown in Fig. 4. The best

linear fit as determined by the least-squares method can be represented by
$MASI = -1.785 + 0.116 * MAMI; r^2 = 0.836, p = 0.0001$

Adverse reactions

Cutaneous reactions were the only side effects noted throughout the study and were limited to mild erythema and/or peeling in the area of application. This was experienced in 4 (27%) of the 15 patients receiving isotretinoin and none (0%) of the 15 vehicle-treated patients in the first two weeks. However, the skin irritation disappeared after 4 weeks. No patients experienced hyperpigmentation or gross depigmentation.

DISCUSSION

This study shows a statistically significant reduction of the severity of melasma demonstrated by MASI and MAMI scores after 12 weeks in both the isotretinoin- and vehicle-treated groups when compared to their baseline ($p<0.02$, Fig. 2, 3). The results of this indicate that daily use of broad spectrum sunscreen has a significant lightening effect on melasma especially in tropical countries where people are exposed to sunlight throughout the year.

After 40 weeks, the average MASI and MAMI score of the isotretinoin-treated group decreased by 68.2 per cent and 47 per cent respectively which was more than the reduction of the MASI and MAMI score of the vehicle-treated group (60%, 34%) (Fig. 2, 3). Although, there was no statistically significant difference between the isotretinoin and vehicle groups, the reductions of the MAMI score seem to be more rapid in the isotretinoin group than the vehicle group after week 24 (Fig. 3).

Cutaneous retinoid reactions such as mild transient erythema and/or peeling occurred in 27 per cent of patients receiving isotretinoin. The retinoid dermatitis disappeared after continuous use of isotretinoin gel. The incidence of retinoid dermatitis in our study seems to be lower than in a previous study using tretinoin cream which had an incidence between 67 per cent and 88 per cent[7,8].

The MASI and MAMI were found to be a simple and useful tool to assess the effects of treatment, and to be superior to global evaluation. The MASI score is not an "exact" numeric value, because the severity rating is subjective. The objective measurement of skin pigmentation such as melanin index may improve the assessment accuracy of melasma severity. By using the MAMI formula, which includes melanin index and area, this score may be more reliable. Moreover, we found that the relation between the MASI and MAMI score was very good ($r^2 = 0.836$, $p = 0.0001$), as shown in Fig. 4. We found it to be a good basis for judging the effect of treatment, particularly when a limited number of patients is involved, as was the case in our study.

The average age of the patients at onset of melasma was 30 years, with a range of 20 to 48 years. This is similar to the recent study of melasma in Caucasians,[7] but differs from another study of melasma in black people,[8] in which the average age at onset was older, namely 44 years. With regard to the distribution of melasma, 14 (47%) of the patients in our study had a malar distribution and 13 (43%) of our patients had centrofacial distribution. This is in contrast to previous studies in Caucasians and black people, in which the centrofacial and malar distribution were predominant, respectively[7,8]. With regard to the type of melasma by Wood's light, 26 (87%) of our patients had mixed type. This is in contrast to previous studies in which the epidermal type was predominant in Caucasians (94%)[7]. In black people, however, all three types are equally found[8]. A strong family history of melasma was present in 16 (53%) of the patients in our study, which is in agreement with the findings of other studies[1,7,8] and suggests an important genetic factor in the pathogenesis of this condition.

This study demonstrated that daily use of broad spectrum sunscreen has a significant lightening effect on melasma especially in tropical countries. Although, the reductions of the severity of melasma seem to be more in the isotretinoin group than in the vehicle group, there was no statistical significance. It is possible that the sunscreen effect was strong and that the isotretinoin could not overcome this effect. It is also possible that isotretinoin is much less effective than tretinoin in this condition. A larger number of cases and a longer follow-up are required for assessing the efficacy of topical isotretinoin.

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การรักษาฝ้าด้วยยาทาไอโสเตรติโนอินในคนไทยเทียบกับครีมไร้ตัวยา

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ฝ้าเป็นภาวะที่มีผื่นดำที่หน้าพบได้บ่อยในคนตะวันออกที่ยังไม่ทราบสาเหตุแน่นอน การรักษาที่มีอยู่ยังไม่ได้ผลดีนัก จากการศึกษาเร็วๆนี้พบว่า tretinoin (all-trans-retionic acid) สามารถทำให้ฝ้าจางลงได้อย่างมีนัยสำคัญ อย่างไรก็ตามการรักษาดังกล่าวทำให้เกิดอาการระคายเคืองกับผู้ป่วยจำนวนมาก คณะผู้นิพนธ์ได้ทำการศึกษาผู้ป่วยชาวไทยที่เป็นฝ้าที่มีความรุนแรงปานกลางถึงมากจำนวน 30 ราย โดยใช้ isotretinoin gel 0.5% (isotrex) เทียบกับครีมไร้ตัวยาร่วมกับการใช้ครีมกันแดด (SPF 28) ทาทุกวันทั่วหน้า เป็นเวลา 40 สัปดาห์ ประเมินผลโดยลักษณะทางคลินิก (ใช้การให้คะแนน Melasma Area and Severity Index) (MASI) และใช้เครื่องวัดสีผิว colorimetry แล้วนำมาคำนวนหา Melasma Area and Melanin Index (MAMI). ผลปรากฏว่าหลังจากการรักษา 40 สัปดาห์ คะแนนเฉลี่ยของ MASI และ MAMI ในกลุ่มที่ได้ isotretinoin ลดลงประมาณ 68.2% และ 47% ตามลำดับเทียบกับ 60% และ 30% ในผู้ป่วยที่ได้ครีมไร้ตัวยา ซึ่งไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ แต่เมื่อเปรียบเทียบค่า MASI และ MAMI ก่อนและหลังรักษาทั้งด้วย isotretinoin และครีมไร้ตัวยาร่วมกับครีมกันแดด ปรากฏว่าค่า MASI และ MAMI น้อยลงอย่างมีนัยสำคัญทางสถิติที่สัปดาห์ที่ 4 และ 12 เราพบว่าค่า MASI และ MAMI มีความสัมพันธ์กันอย่างดี สำหรับผลข้างเคียงของการรักษาพบว่ามีอาการระคายเคืองเล็กน้อยเมื่อรักษาด้วย isotretinoin พบประมาณ 27% โดยสรุปการศึกษานี้พบว่าการใช้ครีมกันแดดมีผลต่อการรักษาฝ้าโดยเฉพาะกับประเทศในเขตร้อนชื้น อย่างไรก็ตามคณะผู้นิพนธ์ไม่พบความแตกต่างของการรักษาด้วย isotretinoin เทียบกับครีมไร้ตัวยา

คำสำคัญ : ฝ้า, การรักษา, ไอโสเตรติโนอิน

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