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A Dermoscopic Evaluation of Melasma Treated with Tranexamic Acid

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Abstract

BACKGROUND: Melasma is a great challenge to the dermatologist. Choosing the proper treatment and the evaluation method are hard issues. Tranexamic acid (TA) injections showed promising results. The dermoscope is a non-invasive handheld tool.

AIM: The objective of the study was to evaluate the efficacy of TA injections in the management of melasma and to assess a new dermoscopic score for the assessment of melasma severity.

PATIENTS AND METHODS: Twenty-seven patients were enrolled in the study. They were assessed clinically and by dermoscopy. An intradermal tranexamic acid was injected on the melasma. Melasma Area and Severity Index (MASI) was used to assess the melasma.

RESULTS: High significant difference was found between pre- (4.700 ± 2.1213) and post-treatment (2.811 ± 2.0870) values of MASI score (p = 0.0001). Clinically, TA treatment showed a dramatic improvement in MASI.

CONCLUSION: The intradermal usage of TA can actually decrease improved the melasma. This was confirmed by the MASI scores and the dermoscope. The dermoscope could be considered as a useful objective score for melasma.

Introduction

Melasma is a disturbed melanocyte activity affecting mainly the face. Other extra-facial sites may be also affected. This condition presents by hyperpigmented macules or patches [1]. Females are affected more than males by 7–8-fold. Darker complexion and outdoor worker personalities are more prone to be affected irrespective of their sex [2].

Sun exposure and hormonal disturbance are of the most important multifactorial reasons for causing melisma [3]. The pathogenesis is still unknown, but some theories suggested that the triggering factor as activated reactive oxygen species (ROS) [4] causes an injury to keratinocytes and fibroblasts followed by tyrosinase stimulation and melanin excretion [4]. Moreover, the vascular endothelial growth factor (VEGF) is stimulated, leading to angiogenesis [5]. The psychological impact as well as the resilient nature of disorder necessitate numerous therapeutic options [6]. Topical applications as Kligman's formula, chemical peels, important modalities in the treatment of melasma [7], and combination of both were highly recommended to overcome the resistant type [8]. However, none of these modalities were free of drawbacks. That is why the searching for effective, safe, and valid one is still a challenge [8].

Tranexamic acid (TA) is promising in the treatment of melasma. It was discovered while treating hemorrhage and chronic urticaria [9]. Its role in the treatment of melasma is through inhibition of plasmin activity that was induced by UV in skin keratinocytes, hence, blocking keratinocyte plasminogen binding. Consequently, it decreases the free form of arachidonic acid (AA) which is the keystone of prostaglandin manufacture necessary for upgrading of tyrosinase activity. Furthermore, the downregulation of VEGF is another important role of TA in reducing the vascular component of melasma [10]. The advantages of TA such as its application by different routes, its validity, and efficacy played a pivotal role in resistant melasma [11], [12], [13]. Evaluation of melasma improvement to any treatment modality objectively was difficult, as the methods were either expensive or invasive, for example, spectrophotometry which needs skin biopsy. On the other hand, using subjective evaluation is easy but inaccurate. That's why in this research, dermoscopy was used as an objective, accurate, recent, noninvasive, and effective and a non-expensive tool [12].

Dermoscopic findings of melasma are classified based on the histopathological subtype

of melasma as follows: In epidermal subtype, dermoscopic assessment discloses well-defined, dark brown pigmented networks with very well delineations of margins. When pigmentation is concentrated in the lower part of the epidermal layers, then dermoscope discloses lighter brown colored networks, in addition to prominent telangiectasias in case of the presence of vascular component. In dermal subtype, ill-defined and imprecise pigmented networks with brown to grayish colors are visualized in addition to annular, honeycomb, or arcuate structures and brownish or grayish granules corresponding to groups of melanophages. Whereas, mixed type shows a combination of all features [14]. The aim of this study was to assess the usefulness of dermoscopy as an objective tool using MASI in assessment melasma in the follow-up of treated melasma with intradermal injection of TA.

Patients and Methods

This is a prospective study. The research ethical committee approval for this research was obtained (Cu-NILES/14/21) of the National Institute of Laser Enhanced Sciences (NILES) which was obtained. Twenty-seven melasma patients were recruited from the outpatient clinic of NILES at Cairo University. Both sexes were included. Their ages ranged from 35 to 65 years. Lactation, pregnancy, and patients on concomitant use of bleaching creams or hemocoagulase agents were excluded from the study. Furthermore, patients with cerebrovascular diseases, clotting disorders, or cardiovascular conditions were also excluded from the study. Full examination was done and informed written consent was obtained for each patient. Risk factor, skin type, melasma duration, and type (malar, temporal, frontal, or centrofacial) were determined for each patient.

Treatment protocol

Melasma was intradermally injected with TA (Kapron ampoule with 500 mg/5 ml produced by Amoun in Egypt) by an insulin syringe with 1 cm apart amongst all injection points. Four milligrams of TA were diluted with 1 ml of normal saline, by 500 mg of TA are in 5 ml. Hence, 100 mg of TA are in 1 ml constitutes 100 units of insulin syringe, so each mg is in 1 unit of insulin syringe, and 4 mg are in 4 units of insulin syringe, and consequently, 4 mg are in 0.04 ml.

EMLA cream was topically applied as an anesthetic cream (EMLA; AstraZeneca, Södertälje, Sweden) 60 min earlier to the intradermal injection. Patients were injected every 2 weeks for a maximum of four sessions. Post-procedural skin care consisted of ice packs or cold compresses, topical emollients, and sunscreens. Every patient was informed to avoid strictly any systemic or topical measures for their facial melasma during the study.

Evaluation methods

Clinical evaluation

Photographic records using similar camera settings, lighting properties, as well as patient sitting were obtained at starting point and 2 weeks after the last session (Figure 1). The improvement was logged through a quartile grading scale: 76–100% excellent; 51–75% very good; 26–50% good; 1–25% fair; and 0% no improvement.

Melasma area and severity index (MASI) score

The intensity and extension of melasma were evaluated by the MASI earlier to treatment and 2 weeks after the last sitting. According to MASI score, the entire face is divided into four areas: The forehead, right malar, left malar, and chin, corresponding to 30%, 30%, 30%, and 10% of the total face area, respectively. The grade of melasma severity was calculated by three variables: The percentages of total area involved, on a scale of 0 (no involvement) to 6 (90–100% involvement); darkness, on a scale of 0 (absent) to 4 (maximum); and the homogeneity of hyperpigmentation, on a scale of 0 (minimal) to 4 (maximum). The MASI was determined by the following equation: MASI = $0.3\ (D_F + H_F)A_F + 0.3(D_{MR} + H_{MR})A_{MR} + 0.3(D_{ML} + H_{ML})A_{ML} + 0.1(D_C + H_C)A_C$ where D stands for darkness, H for homogeneity, A for area, F for forehead, MR for the right malar, ML for the left malar, and C for chin. The values 0.3, 0.3, 0.3, and 0.1 are the respective percentages of the total facial area. A high MASI score relates with severe hyperpigmentation. This score can reach a maximum of up to 48 [15].

Dermoscopy assessment

Three features were assessed by dermoscopy: Dermal, epidermal pigments, and vascularity (Figures 2 and 3). Estimation was done for patients suffering from the malar subtype of melasma. The dermoscope utilized was (DermLite Π Pro HR; 3 Gen, San Juan Capistrano, CA, USA, ×10). It was joined to a camera (Kodak 14 megapixel with 4× zoom; Kodak, New York, NY, USA). Evaluation was done at baseline and 2 weeks after the last session.

Dermoscopic findings of melasma are classified based on the histopathological subtype of melasma as follows: In epidermal subtype, dermoscopic assessment reveals well-defined, dark brown pigmented networks with very well delineations of margins. When pigmentation is concentrated in the lower part of the epidermal layers, then dermoscope

discloses lighter brown colored networks, in addition to prominent telangiectasias in case of the presence of vascular component. In dermal subtype, ill-defined and imprecise pigmented networks with brown to grayish colors are visualized in addition to annular, honeycomb, or arcuate structures and brownish or grayish granules corresponding to groups of melanophages. Whereas, mixed type shows a combination of all features [14].

Patients' satisfaction

Outpatients were inquired to record their contentment as following: Very satisfied, satisfied, and partially satisfied, fourteen days after the last session. Furthermore, patients were inquired to report any adverse or side effects.

Statistical analyses

The overall analyses were completed by the use of IBM SPSS v.24 (Armonk, N.Y., USA). Continuous quantitative data were summarized using mean ± SD. Main effects were assessed by the use of paired t-test. ANOVA test was carried between one side before treatment, after treatment, and the control to detect if there were any significant differences between the three groups, unpaired t-test, Pearson correlation, and also, responsiveness to treatment and clinical change from starting baselines to the ends of treatment were evaluated by paired t-test on MASI scores. Calculation of effect size of both was also performed. $p < 0.05$ was considered statistically significant.

Results

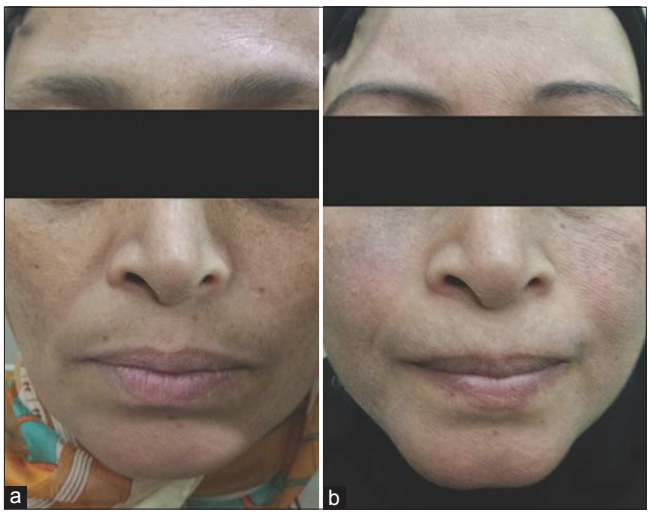

Figure 1: A female patient 42 years old with melasma due to oral contraceptive pills intake. (a) Front view before treatment with TA. (b) Front view after treatment with TA

Twenty-seven melasma patients were recruited for this work. One patient did not continue for the reason that she lived far away and could not come on regular basis. Twenty-six patients; 23 females (88.46%) and 3 males (11.54%) continued this research.

Table 1: Patient demographic data and characteristics

Study parameters	Values
Age (mean ± SD)	43 (± 6.2)
Sex (n, %)	
Males	3 (11.54%)
Females	23 (87.9%)
Skin type (n, %)	
II	2 (7.69%)
III	17 (65.38%)
IV	7 (26.92%)
Risk factors (n, %)	
Actinic	19 (73.07%)
Hormonal	3 (11.53%)
Actinic and hormonal	2 (7.69%)
Oral contraceptive pills	2 (7.69%)
Clinical type (n, %):	
Temporal	3 (11.53%)
Malar	20 (76.92%)
Centrofacial and frontal	3 (11.53%)
Melasma duration (mean ± SD) (years)	5.22 ± 5.62

Their ages ranged from 30 to 60 with a mean of 44 ± 6.3 years. Patients' characteristics and demographic data are presented in Table 1. Finally, 13 patients (50%) reported high satisfaction when treated with TA (Table 2).

Table 2: Patient satisfaction

Patient satisfaction	Frequency (%)
Not satisfy	0 (0.0%)
Partially satisfied	6 (23%)
Satisfied	7 (26.9%)
Highly satisfied	13 (50%)
Total	26 (100.0%)

MASI scores

The MASI results showed a significant dramatic improvement when compared the TA treated side to the baseline ($p = 0.00002$) (Table 3). The dermoscopic evaluation showed a significant reduction of all components of melasma. Epidermal, dermal, and vascular components were reduced in comparison to the baseline.

Table 3: Comparing MASI before and after treatment

Parameter	Before treatment Mean (± SD)	After treatment Mean (± SD)	p
MASI	4.70 (± 2.1 2)	2.81 (± 2.08)	0.000002*

*p < 0.05 is considered statistically significant. MASI: Melasma Area and Severity Index.

Discussion

This study was designed to answer two questions: First, the effect of intradermal TA injection on melasma. The second aim was to evaluate the dermoscope as a reliable easy objective method.

Intradermal TA injection showed a marked improvement of melasma with a better esthetic

appearance. This obtained result was confirmed clinically by MASI. Comparison between the treated sites and the baseline confirmed the results. Hence, as a first objective, this study is trying to answer the question why and how TA did improve melasma. TA acts through inhibition of plasminogen-plasmin system and hence blocking keratinocyte-melanocyte interaction. Eventually, tyrosinase activity, endothelin-1, α-MSH, and basic fibroblast growth factor (bFGF), arachidonic acid and its metabolite PG_2 are reduced [19].

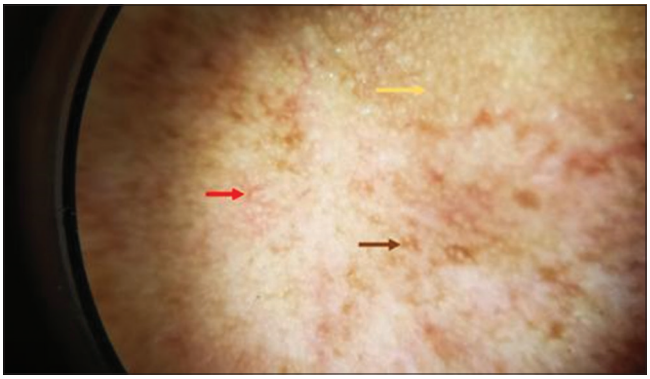

Figure 2: Melasma component (epidermal, dermal, and vascular elements) of the same patient by dermoscopic assessment before treatment of TA (the red arrow points at the vascular component, the brown arrow points at pigment epidermal components while the yellow arrow points at the pigment component at the dermis)

Furthermore, plasmin stimulated single-chain urokinase plasminogen activator (Sc-uPA) which consecutively stimulates melanocytes is decreased. Tyrosinase-related proteins 1 and 2 (TRP1 and TRP2) which have a role in maintenance of melanosomes structure and regulation of melanocyte proliferation and death are as well decreased [20]. Moreover, TA blocks plasmin conversion of the extracellular matrix bound VEGF into its free diffusible form thus hanging up angiogenesis. In addition, it impedes new vessel formation that is induced by basic fibroblast growth factor (bFGF) [13].

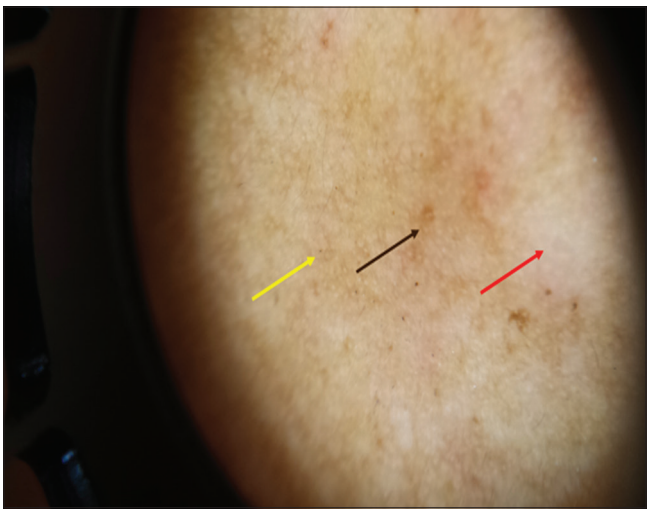

Figure 3: Melasma component (epidermal, dermal, and vascular elements) of the same patient after treatment of TA by dermoscopic assessment (the red arrow points at the vascular component, the brown arrow points at pigment epidermal components while the yellow arrow points at the pigment component at the dermis)

All these mechanisms help in diminution of erythema in melasma [13]. The intradermal TA was considered superior to the oral TA as the later causes hypomenorrhea, GIT symptoms, and cardiovascular manifestations [21]. Furthermore, relapse of melasma occurred within 2 months after stoppage of oral TA [21], [22]. Topical formulations has been tried but with various results and treating only epidermal melasma [22]. Hence, in this study, ID injection was used to get TA directly into the skin aiming to have more response with minimal side effects. Nowadays, dermoscopy is a useful, non-invasive, and an easy handling tool used to evaluate the improvement of melasma objectively. It is helpful to see the pigment colors and their dispersal and the vascular component [16], [17], [18]. Dermoscopically, melasma could be differentiated into its types. It shows very characteristic changes as presence of dark brown color and well-defined network in epidermal type; blue or bluish-gray color when located in the dermis; and presence of both exhibits mixed type [18]. Furthermore, it is not influenced by patient's skin type, vascular, and collagen changes [18]. We accept as true that this score can be a dependable tool in the hands of expert dermoscopists for appropriate valuation of melasma. Hence, as a second aim, this study evaluated the effect of intradermal injection of TA in treatment of melasma using dermoscopy as a cheap and an accurate tool. On the other hand, spectrophotometry used in many studies of melasma is expensive, time consuming, and not easily available. Furthermore, it depends on light reflection in contrast to dermoscopy that relies on direct visualization. Besides, spectrophotometry evaluates only pigmentation and needs skin biopsy which is unesthetic especially in the face and unpleasant for the patients.

Results showed significant improvements at clinical MASI showed a decrease by 40.21% after a 10-week intervention with TA with significant p value (0.000002).

There was a consensus from Saki *et al.* in 2018 who described a split face study, where they compared topical hydroquinone 2% (HQ) on one half of the face and ID injection of TA on the other half of the face [10]. They deduced that once-a-month TA injections were better than everyday HQ in falling the melanin value during the 1st month ($p = 0.013$). As regards the results of our dermoscopic finding, our study is in line with their evidence. However, they used a colorimeter, Dermacatch instead of dermoscopy.

No difference in the results of TX being used orally or intradermal injection as shown in two previous studies. Sharma *et al*. in 2017 compared TA orally (250 mg TDS) with ID injection of TA (4 mg/ml every month) 12 weeks. Both treatment modalities were about equally as effective in reducing MASI (79%). They attributed the slightly better reduction of melasma to the route of application that can reach the mid dermis but they used woods light [11], [24]. However, in this

study, we used ID injection of TA every 2 weeks for 8 weeks with the same concentration.

In 2016, George evaluated the effect of TA microneedling and found that about 41% of melasma patients showed improvement surpassing 50% without any major side effects [20].

The importance of TA concentration was shown in a study done by Pazyar *et al*. when two concentrations of TA (4 mgs/mL and 10 mgs/mL) were compared to the 4% HQ cream. The results revealed that equal improvement concerning the MASI scores in TA 10 mg/ml and the 4% hydroquinone group [25].

However, Elfar and El-Maghraby in 2015, in a comparative study of 60 women compared weekly ID TA injection, topical silymarin cream, and glycolic acid peels, found that TA showed least significant improvement [26].

Khurana in 2019 performed a randomized comparative study for 12 weeks in 64 patients. They compared ID TA (4 mg/ml/month) versus TA orally 250 mg BD and found that oral TA group showed more significant response (57.5%) than ID group (43.5%) which supports our result [27]. However, we get nearly this percent earlier by the 10th week.

On the contrary, Kim *et al.* in 2017 found that the mean of MASI score was noticeably reduced after the use of topically applied TA resulting in a good response rate of about 96% [28]. Clinical results were assessed by the use of the modified MASI (mMASI) as well as a Chromameter. The skin biopsies were got to assess vascularity and pigmentations. Both CD31 numbers and endothelin (ET)-1, which are markers of the vascular and pigments elements, were downregulated. [28]. Atefi *et al.* in 2017 reported a significant patient satisfaction when receiving topical 5% TA (33%) [4] which is less than our finding.

It is worth mentioning that the most important points of strength in this work are the qualitative assessment of melasma by patient's satisfaction and the quantitative assessment done by clinical MASI scores through dermoscopy. It is the first study to assess melasma improvement using dermoscopy through amplifying its elements. It is an objective, non-invasive, and an easy handling approach. Furthermore, it provides a less biased and a more precise determination of changes in the skin. Hence, using both scores can afford a better reflection on the extent of improvement and efficacy attained by any treatment modality for melasma.

Limitations

The limitations of this study included the average sample size that precluded us from drawing more conclusions, as well as the short-term treatment (8 weeks) and follow-up (2 weeks) periods.

Conclusion

The use of dermoscope for the assessment of melasma may have a bright side in the future on the basis as it is simple to use, cheap, and accessible. Furthermore, it may pave the way for more analysis of other hyperpigmented disorders.

The intradermal usage of TA can really decrease epidermal and dermal melanin levels, vascularity, and MASI score with high patient contentment, also it evaluates the element of vascularity which is not calculated in MASI scores. Furthermore, pigmentation is differentiated into epidermal and dermal and this was not considered in MASI score making an advantage to this new score.

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