Research Article

Role of Tranexamic Acid in treatment of Melasma

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Abstract
Introduction: Melasma (chloasma) is a typical hypermelanosis and a common dermatologic skin disease that involves sun-exposed areas of the skin. It mostly affects women of reproductive age. Solar and ultraviolet exposure are the most crucial etiologic factors. **Aim of the work:** The present work has been conducted to evaluate the clinical, histopathological and immunohistochemical changes in melasma patients treated with topical tranexamic acid application using microneedling technique. **Patients and Methods:** The present study was conducted on 21 patients with melasma. They were selected from Dermatology Outpatient Clinic of Minia University Hospital during the period from December 2014 till November 2015. **Results:** The present studyincluded21 cases with melasma, selected from the Dermatology Outpatient Clinic of Minia University Hospital. All of them were females (100%).The age of patients at the time of examination ranged from 25 to 54 years with a mean ± SD of 39.28±7.16years. As regard Fitzpatrick skin type, ten patients (47.6%) were skin type III and eleven patients (52.4%) were skin type IV. **Discussion:** Melasma is an acquired dermatological disease characterized by light to dark brown macules and patches on sun-exposed areas of the skin. It is more prevalent in women with darker skin types. In conclusion, on the basis of the findings, topical TXA can be used as potentially a safe, effective, and promising therapeutic agent for the treatment of melasma. The medication is easily available and affordable. Microneedling can significantly increase the effectiveness of topical TXA in treating melasma, and the combined therapy is safe and painless, without significant side effects and almost no downtime.
Keywords: Arachidonic acid, Area of chin, Adrenocorticotropic hormone

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Introduction
Melasma (chloasma) is a typical hypermelanosis and a common dermatologic skin disease that involves sun-exposed areas of the skin. It mostly affects women of reproductive age. Solar and ultraviolet exposure are the most crucial etiologic factors. Pregnancy, certain endocrine disorders and hormonal treatments, cosmetics, phototoxic drugs, and antiseizure medications are well-known inducing and exacerbating factors (Prignano et al., 2007).

Melasma is classified according to wood's light examination into four major clinical types epidermal, dermal, mixed, and indeterminate. Different treatment options are currently available for melasma. The use of broad-spectrum (UVA + UVB) sunscreen is important. Topical hydroquinone, the most common treatment for melasma. Other 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. Chemical peels, laser treatments, and intense pulsed light therapy are additional therapeutic modalities that have been used to treat melasma. The choice of proper treatment should depend on the type of melasma to be treated, the skin complexion of the patient, possible previous treatments, the expectations and compliance of the patient (Gupta et al., 2006).

Tranexamic acid (TXA) (Trans-4- Amino-methylcyclohex- anecarboxylic acid) is a plasmin inhibitor used to prevent abnormal fibrinolysis to reduce blood loss. It is a synthetic derivative of the amino acid lysine and exerts its effect by reversibly blocking lysine binding sites on plasminogen molecules, thus inhibiting plasminogen activator (PA) from converting plasminogen to plasmin (Horrow et al., 1991).

As plasminogen also exists in human epidermal basal cells (Isseroff and Rifkin,1983) and cultured human epidermal keratinocytes contain tissue type PA (Jensen et al., 1990).

Recent studies have revealed that topical TXA a plasmin inhibitor, prevents UV-induced pigmentation in guinea pigs. Topical TXA inhibits UV-induced plasmin activity in keratinocytes by preventing the binding of plasminogen to the keratinocytes, which ultimately results in decreased free arachidonic acid and a diminished ability to produce prostaglandins, which in turn decrease melanocyte tyrosinase activity (Maeda and Naganuma,1998).

TXA can be used as a new potentially, effective, safe and promising therapeutic agent in melasma. The medication is easily available and affordable (Budamakuntla et al., 2013).
Transdermal delivery has become a popular route of drug delivery in recent years. However, permeation of drugs through skin is limited to small lipophilic molecules. Microneedle technology involves the creation of micron-sized channels in the skin, which can allow the delivery of hydrophilic molecules including large proteins which do not pass the skin barrier passively (Kalluri and Banga, 2009).

Aim of the work

The present work has been conducted to evaluate the clinical, histopathological and immunohistochemical changes in melasma patients treated with topical tranexamic acid application using microneedling technique.

Patients and Methods

The present study was conducted on 21 patients with melasma. They were selected from Dermatology Outpatient Clinic of Minia University Hospital during the period from December 2014 till November 2015.

Inclusion Criteria

Adult female patients with melasma.

Exclusion Criteria

Pregnant females.
Patients with active acne vulgaris.
Immuno-compromising diseases (possibility of delayed healing, increased susceptibility to infection or excessive pigmentation).
Patients with past history of oral contraceptive pills or systemic steroids within 6 months before starting the study.
Patients with bleeding disorders and anticoagulant therapy.

Patients who underwent ablative or non ablative laser treatments, dermabrasion and deep chemical peels in the previous 6 months to the start of microneedling therapy
Patients on chemotherapy, high doses of corticosteroids and radiotherapy.
All patients were subjected to the following;
- Full history taking including; personal history (age, sex and occupation), present history (onset, course and duration of the disease), past history (previous medications) and family history of melasma.
- General, clinical and dermatological examinations.
- Wood's light examination to determine the type of melasma (epidermal, dermal or mixed).
- An informed consent had been obtained from each patient to be enrolled in the study, photographed and biopsied. The procedure, potential complications and realistic expectations were discussed with the patients.
- Photographing of the face before the start of treatment, then before every session and 2 weeks after the last session.
- The patients were instructed to use sunblock sun protective factor (SPF) 50+ for at least 2 weeks before the first treatment session and in between sessions.
- Other concomitant methods of melasma treatment were not allowed throughout treatment period.
- The study was approved by the Committee for Postgraduate Studies and Research of Minia University.

Results

The present study included 21 cases with melasma, selected from the Dermatology Outpatient Clinic of Minia University Hospital. All of them were females (100%). The age of patients at the time of examination ranged from 25 to 54 years with a mean ± SD of 39.28± 7.16years. As regard Fitzpatrick skin type, ten patients (47.6%) were skin type III and eleven patients (52.4%) were skin type IV.

The duration of disease ranged from 6 months to 7 years with a mean ± SD of 10.62±24.22 years. A positive family history was present in 9 patients (42.8 %) out of 21patients (Table2).

Table: The range and mean percentage of reduction of number of epidermal ,dermal and total MART-1 positive stained cells

MART reduction	Descriptive statistics
Epidermal reduction	
No reduction	0(0%)
Yes	21(100%)
Percent of epidermal reduction	
Range	(7.5-89)
Mean ± SD	61.11±19.84
Dermal reduction	
No reduction	2(9.5%)
Yes	19(90.5%)
Percent of dermal reduction	
Range	(33-85.5)
Mean ± SD	60.34±16.61
Total reduction	
No	0(0%)
Yes	21(100%)
Percent of total reduction	
Range	(17.5-87.5)
Mean ± SD	60.71±17.8

Discussion

Melasma is an acquired dermatological disease characterized by light to dark brown macules and patches on sun-exposed areas of the skin. It is more prevalent in women with darker skin types. Although its pathogenesis is not yet clearly defined, some etiological factors have been identified, including genetic background, pregnancy, hormonal therapies and sun exposure. Melasma has a significant psychological impact on the affected patients because of its disfiguring nature (Guinot et al., 2010).

Although multiple therapeutic modalities have previously been tried and touted as being successful, truly efficacious treatment options for this condition have been few and quite elusive. Such treatment approaches include; numerous topical agents, chemical peels, dermabrasion, and a variety of lasers and light-based devices (Gupta et al., 2006).

TXA is one of the treatment strategies for melasma that has been a focus of attention in recent years. Potential mechanisms for its effectiveness include the following: inhibition of melanocyte proliferation (Maeda and Tomita, 2007); inhibition of melanin synthesis in melanocytes (Kim et al., 2015); accelerated recovery of impaired skin barrier function (Yuan et al., 2014); reduced number of blood vessels in the dermis; and reduced number of mast cells in the dermis (Na et al., 2013).

Oral administration of TXA was reported in several studies to be effective for melasma. After oral TXA for 4 months, 89.7% of Korean patients had documented improvement (Lee et al., 2016), and at a dosage of 250 mg twice daily for a therapeutic period of 6 months, TXA was effective in 64.8% of Chinese patients (Wu et al., 2012). Furthermore, a preliminary study of 2 tablets of compounded TXA administered 3 times per day reported that improvement occurred in 85% of patients in 4 weeks, 97% in 8 and 12 weeks, and 100% in 16 weeks (Li et al., 2014). TXA is a synthetic lysine analog that inhibits plasmin activity, which has been used as an antifibrinolytic agent for over 30 years. The side effects of oral TXA remain a concern. In addition to the possibility of gastrointestinal discomfort, headache, and hypomenorrhea, the most important potential risk is systemic thrombosis formation (Krivokuca and Lammers 2011).

In conclusion, on the basis of the findings, topical TXA can be used as potentially a safe, effective, and promising therapeutic agent for the treatment of melasma. The medication is easily available and affordable. Microneedling can significantly increase the effectiveness of topical TXA in treating melasma, and the combined therapy is safe and painless, without significant side effects and almost no downtime.

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