ORIGINAL ARTICLE

Topical tranexamic acid as a promising treatment for melasma

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Background: In recent times, tranexamic acid (TA) is claimed to have whitening effects especially for ultraviolet-induced hyperpigmentation including melasma. The aim of our study was to evaluate the efficacy and safety of topical solution of TA and compare it with combined solution of hydroquinone and dexamethasone as the gold standard treatment of melasma in Iranian women. **Materials and Methods:** This was a double-blind split-face trial of 12 weeks which was conducted in Isfahan, Iran. Fifty Iranian melasma patients applied topical solution of 3% TA on one side of the face, and topical solution of 3% hydroquinone + 0.01% dexamethasone on the other side two times a day. The Melasma Area and Severity Index (MASI) and the side effects were evaluated at baseline and every 4 weeks before and after photographs to be compared by a dermatologist were taken. The patient satisfaction was documented at week 12. **Results:** A repeated measurement analysis was used to evaluate the changes in the MASI score before and after treatments. A significant decreasing trend was observed in the MASI score of both groups with no significant difference between them during the study ($P < 0.05$). No differences were seen in patients' and investigator's satisfaction of melasma improvement between two groups ($P < 0.05$). However, the side effects of hydroquinone + dexamethasone were significantly prominent compared with TA ($P = 0.01$). **Conclusion:** This study's results introduce the topical TA as an effective and safe medication for the treatment of melasma.

Key words: hydroquinone, dexamethasone, Melanosis, therapy tranexamic acid

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INTRODUCTION

Melasma is a common acquired dermatitis of light to dark brown macules and patches involving the sun-exposed areas of the face and neck. This disease is commonly observed in women. Men represent only 10% of cases; however, the clinicohistologic characteristics of the disease are same in both sexes.[1] Although the precise cause of melasma remains unknown, some factors such as genetic susceptibility, ultraviolet (UV) light exposure, pregnancy, sex hormones, contraceptive pills, thyroid disease, cosmetics, phototoxic drugs (e.g., antiseizure medications) have been identified as some common contributing factors in developing melasma.[2] Moreover, some factors influence the function of melanocytes, so they can contribute to the UV-induced pigmentation. These factors include photo-induced hormones, growth factors, and chemical and inflammatory mediators.[3]

Different treatment modalities which include elimination of any possible causative factors, use of sunscreen, hypopigmenting agents, and laser therapy are used. Usually, bleaching agents are prescribed in combination with other therapies, such as tretinoin, topical corticosteroids, or superficial peeling agents.[1,4-7] In recent times, some researchers found that tranexamic acid (TA), a traditional hemostatic drug, has hypopigmentory effect on melasma lesions and also prevents UV-induced pigmentation.[2,8-12]

The intracellular release of arachidonic acid (AA), a precursor of prostanoid, and the level of alpha-melanocyte-stimulating hormone increase as the result of plasmin activity. These two substances can activate melanin synthesis. Therefore, the anti-plasmin activity of TA is thought as the main mechanism of hypopigmentory effect of this agent.[13-15] The result of a clinical trial of localized microinjection of TA proved to be promising. Significant decrease in the Melasma Area and Severity Index (MASI) score with no significant side effects was seen after 8 weeks of microinjection of TA.[2] In another study, Kondou *et al*. found that the TA emulsion had improved the pigmentation in 80% of subjects with melasma and 75% of subjects with freckles.[9] Moreover, in a very recent study, a significant decrease in epidermal pigmentation and reversion of melasma-related dermal changes were seen after using both oral and topical TA of 8 weeks.[11]

The aim of this study was to compare the safety and efficacy of topical solution of 3% TA with topical solution

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of 3% hydroquinone and 0.01% dexametasone for treatment of melasma

MATERIALS AND METHODS

This was a prospective, randomized, double blind split-face trial. The target population was all patients with melasma who refer to all dermatology clinics in Isfahan, Iran from September 2009 to September 2010. Ethical approval based on the ethical guidelines of the 1975 Declaration of Helsinki was obtained from the Isfahan University of Medical Sciences Ethics Committee. We explained the procedures, risks, benefits, and potential side effects of the medications to all patients, and written informed consents were obtained from them before the commencement of the study.

All the patients who are above 18 years and have moderate-to-severe epidermal melasma (moderate melasma means when the color of the melasma lesion is moderately darker than that of the surrounding normal skin and sever melasma is defined as markedly darker discoloration of the melasma lesion than that of the surrounding normal skin[16]) with a malar distribution were included in this study. However, patients being pregnant or nursing women, taking contraceptive pills at the time of the study or during the past 12 months, taking any photosensitizing drugs like non-steroidal anti-inflammatory drug, tetracycline, spiranolactone, phenytoin, carbamazepine, and so on at the time of the study, having any bleeding disorders or taking any kind of anticoagulants, and giving any concurrent therapy for melasma were not included in the study. Moreover, the patients should not use any topical therapy for melasma 1 month before the entry into the study.

A total of 50 Iranian patients were enrolled. Wood's lamp examination was performed at the study entry to determine the type of melasma (epidermal, mixed or dermal). Patients with epidermal melasma were chosen. Patients were allocated to apply A and B solution on the right (RM) and left malar (LM) lesions respectively. The TA and hydroquinone + dexamethasone solutions were packed and coded in identical containers for each patient by a pharmacist and were marked as A or B solution. After the end of the study the codes were opened and it revealed that the code A was for TA and B for hydroquinone + dexamethasone. The topical solutions of 3% teranexamic acid was 3 g teranexamic acid dissolved in 10 cc ethanol 96°, 10 cc 1, 3-butanediol and distillated water up to 100 cc while it was 3 g hydroquinone dissolved in 10 cc ethanol 50°+ vitamin C 2 g + dexametasone 10 mg and distillated water up to 100 cc for hydroquinone + dexamethasone solution. The patient used each solution 2 times a day on each sides of the face for 12 weeks.

The patients were advised to avoid excessive sun exposure, apply a broad spectrum sunscreen with a sun protection factor of 30 or higher in the morning, and reapply the sunscreen every 2 h. Clinical evaluation of melasma's severity was performed at baseline and weeks 4, 8, 12. A subjective measurement based on the area and the severity of the hyperpigmentation determined by Kimbrough-Green *et al*. was used for clinical assessment. According to the MASI, the whole face is divided into four areas: 30% the forehead, 30% RM, 30% LM, and 10% chin (C). The grade of melasma severity was determined by three variables: A = The percentages of total area involved on a scale of 0 (no involvement) to 6 (90-100% involvement), D = darkness on a scale of 0 (absent) to 4 (maximum), and H = homogeneity of hyperpigmentation on a scale of 0 (minimal) to 4 (maximum). The MASI is then calculated by the following equation:

=0.3 (DF + HF) AF + 0.3 (DMR + HMR) AMR + 0.3 (DML + HML) AML + 0.1 (DC + HC) AC

The highest MASI score is 48 which correlate with severe hyperpigmentation. We calculated the MASI score only for malar area.

In order to evaluate patient satisfaction, a scoring system was conducted at the end of the study. The patient's self-assessment of melasma improvement was graded along four scales: 1 = >75% lightening (excellent), 2 = 51-75% (good), 3 = 26-50% (fair), and 4 = 0-25% (poor).

Clinical investigator asked any side effects of TA (gastrointestinal (GI) complaints such as nausea, diarrhea, and abdominal pain…) and hydroquinone + dexamethasone solutions during the study and then registered them in questionnaires.

Photographs were taken (with Canon power shot S3, Cannon components Inc. Japan) in a standardized position at baseline and week 12 so that the clinical investigator can assess melasma improvement according to her experiences. In this case, melasma improvement was graded along four scales: 1 = >75% lightening (excellent), 2 = 51-75% (good), 3 = 26-50% (fair), and 4 = 0-25% (poor) too.

Data were analyzed using Statistical Package for the Social Sciences (SPSS version 18 for windows). A repeated measurement analysis was used to evaluate the changes in the MASI score before and after treatments.

RESULTS

From September 2009 to September 2010, 50 women with melasma were included in this study, although 39 patients successfully completed the trial. Four of the patients became pregnant, two start using contraceptive pills, and five of

them changed their place of resident to another city. The characteristics of 39 participants are summarized in Table 1.

The mean MASI score (mean + standard deviation) of the baseline and all reassessment visits after treatment with TA and hydroquinone + dexamethasone are shown in Table 2. The mean MASI score of the baseline in TA group was 31.68 ± 10.32 while after 12 weeks it reached to 10.76 ± 9.43 ($P = 0.00$). Furthermore, in Hydroquinone + dexamethasone group it was 29.52 ± 11.72 at baseline and after 12 weeks it reached to 10.48 ± 7.84 ($P = 0.00$) [Figures 1-3].

According to repeated measurement analysis, the changes in MASI score were statistically significant during the study period in both groups ($P < 0.05$). However, no significant differences were seen between treatment with TA and hydroquinone + dexamethasone at baseline and all reassessment visits ($P > 0.05$).

Moreover, it was shown that the amount of changes in the mean MASI score of both groups were statistically significant in all reassessment visits ($P = 0.00$) [Table 3].

The patients' self-assessment of melasma improvement was evaluated at week 12; 3%, 27.3%, 30.3%, and 39.4% of patients graded melasma improvement of the side which was treated with TA as excellent good, fair, and poor, respectively, while it was 6.1%, 33.3%, 39.4%, and 21.2% respectively for hydroquinone + dexamethasone. For this results, no statistically significant differences was seen between TA and hydroquinone + dexamethasone ($P = 0.44$) [Figure 4].

Moreover, the physician graded the melasma improvement of patients according to their photos of the base line and week 12. It was 27.3%, 42.4%, and 30.3% as excellent, good, fair respectively for TA and 24.2%, 48.5%, 24.2%, and 3.0% as excellent, good , fair respectively for hydroquinone + dexamethasone. In this case, the Chi-square test showed no significant difference between these two types of treatments ($P = 0.88$) [Figure 5].

The erythema, skin irritation, xerosis, and scaling were the side effects of TA, which were reported by patients. No GI and serious complaints were seen with TA. In addition, patients reported erythema, skin irritation, dryness of the skin, scaling, hypertrichosis, and inflammation as the side effects of hydroquinone + dexamethasone [Table 4]. Significant side effects were noted for hydroquinone + dexamethasone compared with TA ($P = 0.01$).

Table 1: the characteristic of participants

Patients characteristic	Mean ± SD/ frequency (percentage)
Age (year)	40.00±4.63
Age onset of melasma (year) (minimum-maximum)	29.60±8.13 (29-51)
Duration of melasma (year) (minimum-maximum)	10.34±7.18 (3 months-31)
Family history	
+	24 (61.5)
–	15 (38.5)
History of endocrine disease	
+	6 (15.4)
–	33 (84.6)
History of usage of antisolar cream	
+	34 (87.2)
–	5 (12.8)

SD = Standard deviation

Table 2: The mean MASI score (mean ± SD) of the baseline and all reassessment visits after treatment with TA and hydroquinone + dexamethasone

Time	TA group	Hydroquinone + dexamethasone group	*P**
Baseline	31.68±10.32	29.52±11.72	0.49
Week 4	22.60±10.37	19.48±10.93	0.31
Week 8	15.84±12.01	13.40±6.90	0.38
Week 12	10.76±9.43	10.48±7.84	0.91
*P**	0.00	0.00	

*Repeated measure; MASI = Melasma Area and Severity Index; SD = Standard deviation; TA = Tranexamic acid

Table 3: The frequency (percentage) of side effects in two groups

Group	Side effect	
	Yes	No
TA	9 (23.1)	30 (76.9)
Hydroquinone + dexamethasone	20 (51.3)	19 (48.7)

TA = Tranexamic acid

DISCUSSION

The aim of this study was to compare the safety and efficacy of topical solution of 3% TA with topical solution of 3% hydroquinone and 0.01% dexametasone in treatment of melasma. In this study, it was shown that the TA is as effective as the cumulative effect of hydroquinone and dexamethasone in treatment of melasma while it is safer than the gold standard of melasma treatment, hydroquinone.

Trans-4-aminomethylcyclohexanecarboxylic acid (Trans-AMCHA, TA) is prescribed as an antifibrinolytic agent. Its contraindications include acquired defective color vision, an active intravascular clotting condition, and hypersensitivity to TA. Furthermore, it should be carefully prescribed for people with cardiovascular disease, cerebrovascular disease, and simultaneous use of hemocoagulase agents. The common side effects of TA are GI complaints (nausea, diarrhea, and abdominal pain).[2]

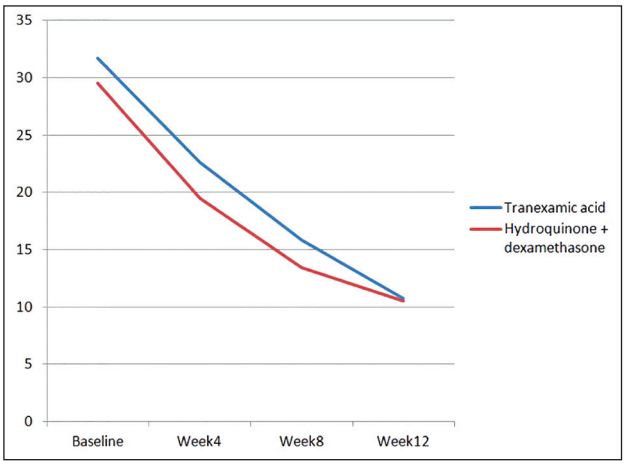

Figure 1: Changes of Melasma Area and Severity Index score of two groups

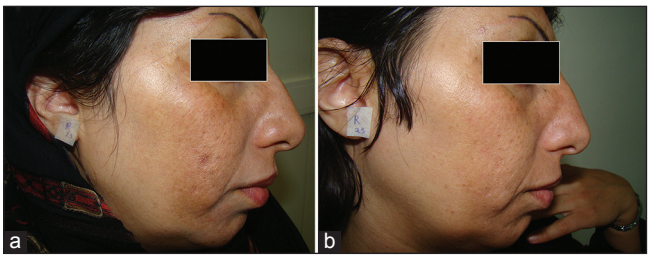

Figure 3: Representative the side which was treated with tranexamic acid (a: At baseline, b: After 12 weeks)

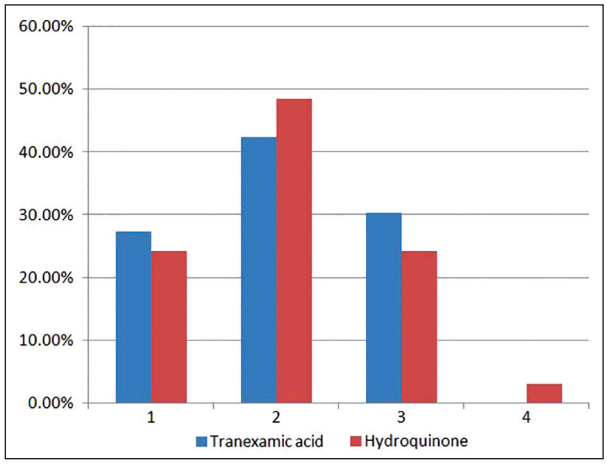

Figure 5: Physician assessment of improvement at week 12 based on the patients photos. Physician were asked to grade their overall improvement as 1 = >75% lightening (excellent), 2 = 51-75% (good), 3 = 26-50% (fair), and 4 = 0-25% lightening (poor)

Some of the metabolites of AA, such as prostaglandin E2, can activate the melanogenesis. Moreover, the release of AA is increased by plasmin in endothelial cells. During UV irradiation, the synthesis of AA and plasminogen activator are induced in keratinocytes. All of these processes result in more melanin production in the skin.[8] The mechanism of TA, which is a lysine analog, in the treatment of UV-induced pigmentation includes interfering with the structure of plasminogen and preventing the binding of plasminogen to

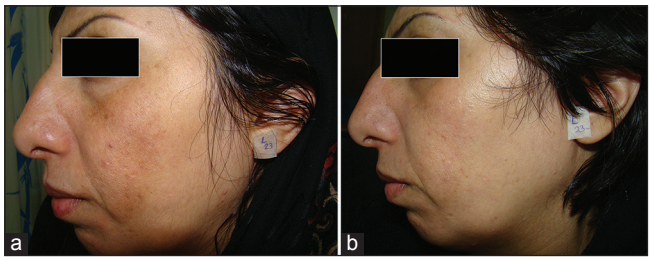

Figure 2: Representative the side which was treated with hydroquinone + dexamethasone (a: At baseline, b: After 12 weeks)

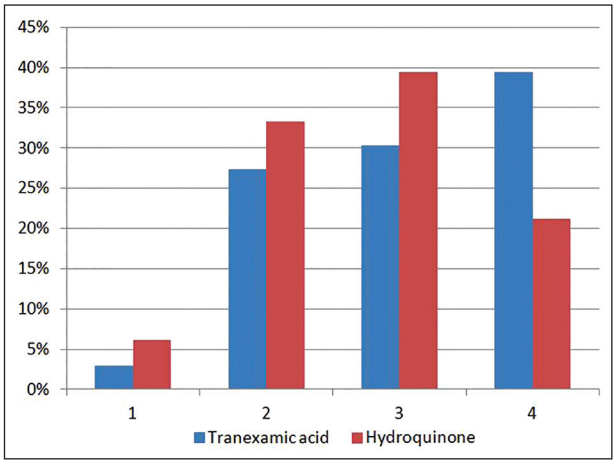

Figure 4: Patient self-assessment of improvement at week 12. Patients were asked to grade their overall improvement as 1 = >75% lightening (excellent), 2 = 51-75% (good), 3 = 26-50% (fair), and 4 = 0-25% lightening (poor)

the lysine-binding sites of keratinocytes. The consequences of such event are less free AAs so a reduced ability to produce prostaglandins and thus decreased melanocyte tyrosinase activity and melanogenesis.[8]

Some studies have confirmed the effectiveness of TA in treatment of melasma. WU *et al*. demonstrated the total improvement rate of 80.9% in 256 patients with melasma by long-term (6-15 months) oral administration of TA. There was no obvious side effect of the treatment except for GI reaction in 4.3% patients and hypomenorrhea in 3.5% patients[17] recently a case-control trial confirmed the lightning effect of oral TA in combination with intense pulsed light and laser treatment in melasma while no serious side effect was reported for it. This study claimed that the such modality is more beneficial during the period of relative high sun exposure like summer.[10] In addition, in a very recent 8 week study, the use of two TA tablets three times a day along with the use of topical TA twice a day showed both significant decline in epidermal pigmentation and improvement of melasma dermal changes.[11] As well, the effectiveness and safety of 6 months oral administration of TA for melasma patients was shown by Wu *et al*.[12]

In another clinical trial, the researchers showed the efficacy and safety of localized microinjection of TA. They concluded

that the such method had little systemic absorption or no systemic side effect.[2] Additionally, Kondou *et al*. have published the results from a clinical study which was examined topical TA emulsion for the treatment of melasma and freckles.[9] The study involved 33 subjects, 25 with melasma and 8 with freckles, who applied the TA emulsion for 5-18 weeks. The results showed not only the whitening effect of topical TA on melasma and freckles through inhibition of melanin synthesis, but also its preventive effect on the appearance of new pigment spots and freckles.[9]

There has not been any study which compared this new treatment with the gold standard one, hydroquinone. It is noteworthy to say that the formula for hydroquinone in our study had dexamethasone which not only has depigmenting effect, but also reduce the inflammation caused by hydroquinone.[18] Therefore, it can be concluded that the TA is as effective as the cumulative depigmenting effects of hydroquinone and dexamethasone.

However, one of the limitations of this study was the lack of objective measurement for pigment reduction. With the use of MASI score, we tried our bests to evaluate an agent's effectiveness. Finally, we concluded that topical TA can be used as a part of melasma treatment without significant side effects which lead to quite good results.

Finally, it was concluded that topical solution of TA seems to be a potentially new medication which can lead to quite rapid results without significant and serious side effects for melasma, especially for the epidermal type. Further studies are required to find out the frequency of usage, long-term benefits, and combination therapy with other medications and methods of melasma treatment to find the additive effect of it. Moreover, the use of an objective method of measurement such as a colorimeter is encouraged for precise quantification of the differences in pigmentation after treatment.

AUTHORS CONTRIBUTION

BE, FFN: Substantial contributions to the conception or design of the work or interpretation of data for the work. Fatemi Naeini: Drawing the work or revising it critically for important intellectual content. Ebrahimi, Fatemi Naeini: Final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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