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Efficacy of localized intradermal microinjection of tranexamic acid at a concentration of 4 mg/ml in the treatment of melasma in Syria

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Abstract: Background: Melasma is a common acquired hyperpigmented dermatosis due to a disorder in the function of the melanogenesis process. Nowadays, there are many used treatments for melasma but it is still a big cosmetic problem.

The Aim of our study is to evaluate the efficacy and safety of intradermal microinjection of tranexamic acid TXA in the treatment of melasma in Syrian women.

Methods: A total of 34 women with melasma, attending Tishreen University Hospital in Lattakia-Syria from January 2020 to January 2021 were included in this prospective (before and after) study. We applied topical anesthesia then we injected 0.05 ml TXA (4 mg/ml) intradermally into the melasma lesions at 1 cm intervals by using a 30-gauge insulin syringe. We repeated this procedure every 2 weeks for 12 weeks. A clinical investigator evaluated the results by using the modified Melasma Area and Severity Index (mMASI) at baseline and at 4, 8, and 12 weeks. Patients were followed up after 3 months from completing the treatment.

Results: The mean mMASI scores decreased from 6.99±3.4 at baseline to 5.98±3.2, 4.59±2.5 and 3.49±2.3 at weeks 4, 8, 12 respectively. This decrease was clinically and statistically significant with a p-value = 0.0001.

Our patients did not show serious side effects.

Conclusion: According to that, we suggest that localized intradermal microinjection of tranexamic acid at a concentration of 4 mg/ml is an effective and safe therapeutic method for melasma.

Keywords: Melasma, mMASI, tranexamic acid TXA.

فعالية الحقن الدقيق الموضعي داخل الأدمة لحمض الترانكساميك بتركيز 4 ملغ/ مل في علاج الكلف

هبه غسان المنصور

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كلية الطب || مشفى تشرين الجامعي || سوريا

المستخلص: الكلف هو مرض جلدي حميد مكتسب مفرط التصبغ شائع، ناجم عن اضطراب وظيفي في اصطناع الميلانين. بالرغم من وجود العديد من العلاجات المستخدمة حالياً، إلا أنه لا يزال يشكل تحدياً تجميلياً كبيراً.

هدف البحث: إلى تقييم فعالية وأمان الحقن الدقيق داخل الأدمة لحمض الترانكساميك TXAفي علاج الكلف عند النساء في سوريا.

طريقة البحث: شملت هذه الدراسة المستقبلية (قبل وبعد) 34 سيدة مصابة بالكلف راجعت مشفى تشرين الجامعي في اللاذقية – سوريا من كانون الثاني 2020 حتى كانون الثاني 2021. بعد تطبيق مخدر موضعي تم حقن 0.05 مل TXA (4 ملغ/ مل) داخل الأدمة

ضمن آفات الكلف بفواصل 1 سم وذلك باستخدام محقنة أنسولين ذات سعة 1 مل وقياس إبرة 30. كرر هذا الإجراء كل أسبوعين ولمدة 12 أسبوع. قام أحد المحققين السريريين بتقييم النتائج باستخدام مشعر مساحة وشدة الكلف المعدل mMASI في بداية الدراسة وفي الأسابيع 4، 8 ،12. تمت متابعة المرضى بعد 3 أشهر من انتهاء العلاج.

النتائج: انخفض متوسط درجات mMASI من 3.4±6.99 في بداية العلاج إلى 3.2±5.98، 2.5±4.59، 2.3±3.49 في الأسابيع 4، 8، 12 على التوالي. كان هذا الانخفاض ذا دلالة سريرية وإحصائية هامة مع قيمة P-value=0.0001. الآثار الجانبية ضئيلة وجميع المرضى تحملوا العلاج بشكل جيد.

الخلاصة: نقترح بناءً على هذه النتائج أنه يمكن استخدام الحقن الدقيق الموضعي داخل الأدمة لحمض الترانكساميك (4 ملغ/ مل) كطريقة علاجية فعالة وآمنة لعلاج الكلف.

الكلمات المفتاحية: الكلف، مشعر mMASI، حمض الترانكساميك TXA.

Introduction.

Melasma is a common acquired hyperpigmented disorder, characterized by symmetric light to dark brown or brown- gray patches or/and macules with an irregular outline. Appear primarily on sun-exposed areas of the body most commonly on the face. Forearms and mid - upper chest are less common [1]

It is most prevalent among young to middle-aged women with Fitzpatrick skin types III to V of Hispanic, Asian, African or Middle Eastern race. [1, 2] It can also occur in men in some cases. [3, 4]

Based on Wood's lamp examination, melasma can be classified according to the melanin content as follows. [5] epidermal type which there is an excess of basal and suprabasal melanin, which absorb the light to produce color emphasis in melasma areas. In dermal type, such emphasis is not obvious. In mixed type, there are melanin deposits in both dermis and epidermis so that the color emphasis is clear in just a few sites. In people with V and VI Fitzpatrick skin types, the color emphasis at areas of melasma is even unnoticed using Wood's light examination. On the face, melasma presents as centrofacial, malar, and mandibular. [4]

Exacerbating factors include sun exposure, genetic susceptibility, pregnancy, hormonal therapies, photosensitizing drugs, antiseizure medications and cosmetics. [1, 2, 6, 7, 8] The most common factors are sun exposure, pregnancy, and use of oral contraceptives. [1]

Nowadays, many treatment methods with different rates of safety and effectiveness are used in melasma treatment. They include topical medications such as Hydroquinone, retinoic acid and steroids whether they have been used alone or with each other (Kligman'triple combination). [9, 10, 11] Other lower efficacy treatments are azelaic acid, kojic acid, ascorbic acid, glycolic acid.[12-17] Procedural treatment like chemical peels [12], microdermabrasion, and light-based options like Q-switched Nd: YAG laser, intense pulse light can also be used. [13, 14]

These treatments have many side effects which restrict their usage like: erythema, skin irritation, sensitivity to sunlight, dryness, exogenous ochronosis, desquamation, atrophy, telangiectasia and hypertrichosis. [16, 18]

Recently, many studies have shown the efficacy of TXA in reducing the pigmentation of melasma lesions and preventing Ultraviolet radiation-induced pigmentation whether it has been used orally, topically, or intradermally, with minimal side effects.

The chemical composition of tranexamic acid (TXA) is Trans – 4–Amino methyl-cyclohexane carboxylic acid. Its effect was first discovered by Nijo Sadako In 1979 while he was treating a case with both melasma and chronic urticaria. [19]

TXA is synthetically similar to the amino acid lysine, which reversibly blocks lysine- binding sites on plasminogen molecules preventing plasminogen activator from converting plasminogen to plasmin in keratinocytes and thus inhibiting fibrin dissolution and reducing bleeding. The anti-plasmin activity of TXA is the main mechanism of its hypopigmentant effects because plasmin inhibition prevents the release of arachidonic acids which stimulate the melanogenesis. TXA can also inhibit tyrosinase activity by having a partially similar structure to tyrosine. [20] It can also reduce erythema and vasculature seen in melasma areas by converting vascular endothelial growth factor (VEGF) to a diffusing form and decrease dermal mast cells number. [21-22]

Intradermal microinjection (mesotherapy) is a medical technique that uses intradermal or subcutaneous microinjection of a diluted medical substance into the mesoderm. [23]

The objective of our study is to evaluate the efficacy and safety of intradermal microinjection of tranexamic acid at a concentration of 4 mg/ml in treating melasma in Syrian population.

Patients and methods.

This is before and after (prospective) clinical trial. 34 Women with melasma who attended dermatology department-outpatient clinic of Tishreen university hospital, Lattakia, Syria from January 2020 to January 2021 were included in our study.

Before starting and after explaining the procedure, advantages and possible side effects, we took written consent from all patients. This study was performed under the Declaration of Helsinki.

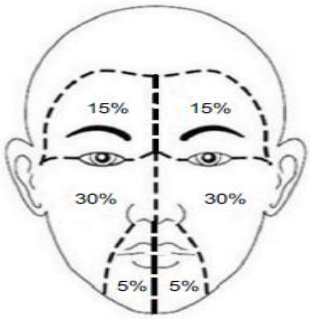
The inclusion criteria were patients with age above 18 years with any melasma severity. The exclusion criteria included pregnancy and lactation, patients on oral contraceptive pills or hormone replacement therapy, any known coagulant disorder or current usage of anticoagulants or antiseizure medications, hypersensitivity to TXA, patients with current active acne lesions or any systemic or local infection to the area to be treated, history of any melasma treatment in the last month before participation into the study and history of keloid formation.

After obtaining personal and demographic history such as name, age, sex, address, contact number, occupation, any disease history, family history of melasma, age of onset, duration and progress of melasma, precipitating factors, site, type of melasma, skin type according to Fitzpatrick's classification. We performed Wood's lamp examination to determine the type of melasma (epidermal, dermal or mixed).

We performed a modified MASI (melasma area and severity index) scoring system to assess melasma severity at the beginning of the study (baseline) and weeks 4, 8 and 12.

We calculated it by the equation: mMASI= 0.3(D)(A) + 0.3(D)(A) + 0.3(D)(A) + 0.1(D)(A)

A refers for area, **D** refers for darkness (the details are in figure 1 and table 1 and 2)



mMASI= 0.3(D)(A)+0.3(D)(A)+0.3 (D)(A)+0.1(D)(A)

Range 0 – 24

Figure (1) Face division and modified MASI equation. [24]

Table (1) How to calculate mMASI in each location of the face.

Location of melasma	Scoring
Forehead	0.3✕A✕D
Left cheek	0.3✕A✕D
Right cheek	0.3✕A✕D
Mandibular	0.1✕A✕D

Table (2) How to determine the darkness (D) and the area (A) in mMASI equation.

Darkness (D)	Area (A)
0 = absent	0 =no involvement
1 = slight	1 = < 10
2 = mild	2 = 10 – 29
3 = marked	3 = 30 - 49
4 = severe	4 = 50 – 69
	5 = 70 – 89
	6 = 90 - 100

We took photographs of the patients before treatment and after 12 weeks. All patients had complete blood count (CBC) and coagulation tests (INR, PT, PTT) before starting.

Tranexamic acid is available as 5 ml /500 mg ampoule. We prepared it by draining 4 mg (units) of TXA in a 100 unit/ml insulin syringe and completing it to 100 units with normal saline to get the right concentration (4 mg/mL).

After wiping the area to be injected with alcohol, we applied topical anesthesia (lidocaine 2.5% / prilocain 2.5%) (COSMOCAINE PLUS) cream over it for about an hour before the procedure.

A 30-gauge, 1 mL insulin syringe with 4 mg/mL TXA was intradermally injected every 1cm of melasma area. We used about 0.05ml in each site. This was repeated every two weeks for 12 weeks.

Every patient was advised to use a broad-spectrum sunscreen with more than 30 SPF (sun protection factor) and to avoid sunlight as much as possible.

Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 20. Basic Descriptive statistics included means, standard deviations (SD), median, frequency and percentages. Friedman test to compare the mean of several related groups. One-way ANOVA test is to study the difference between the means of more than two groups. Differences of distribution were examined by using the fisher exact test. P-value < 0.05 was considered as statistically significant.

The results.

All the 34 patients who presented to the department of dermatology from January 2020 to January 2021 completed the study.

Their ages ranged from 25 to 51 years old with a mean±SD (37.85±7).

Duration of melasma ranged from 1 to 11 years with a mean±SD (4.82±2.9).

Patients had Fitzpatrick's skin type III or IV.

Twenty-four patients (70.6%) were treated for melasma by either chemical peels or skin-whitening products in the past (Not in last month before the study).

The mean mMASI scores at baseline and weeks 4, 8, 12 are shown in table 4 and figure 2.

Changes in the mMASI scores were statistically significant at weeks 8 and 12 (p-value < 0.05).

The declines (improvements) in the means of mMASI scores were 14.4%, 34.3% and 50% at weeks 4, 8, 12 respectively.

Each patient was followed up after 3 months to check on any relapse.

Three patients (8.8%) had mild relapse (2.18% increases in mean mMASI scores) at week 24 (end of follow- up period).

No serious side effects apart from mild pain during injection, erythema and mild wheal were observed which lasted for 1-2 hours in most patients.

The percentages of improvement were higher in epidermal type of melasma than mixed type.

Table (3) Demographic and basic information of patients.

Number of the patients	34
Age (years) (mean ± SD)	33.02±5.3

Number of the patients	34
Fitzpatrick skin type (number, %)	
Type III	13(38.2%)
Type IV	21 (61.8%)
Melasma Type (number, %)	
Epidermal	30 (88.2%)
Mixed	4 (11.8%)
Pattern of distribution (number, %)	
Centrofacial	23 (67.6%)
Malar	11 (32.4%)
Family history (number, %)	
Negative	15 (44.1%)
Positive	19 (55.9%)

Table (4) mean mMASI scores and p-value at baseline and weeks 4, 8 and 12 according to friedman test.

	Mean±SD (mMASI)	Range	P-value
Week 0 (baseline)	6.99±3.4	1.20-15	0.0001
Week 4	5.98±3.2	1.20-14.60	
Week 8	4.59±2.5	1.20-14.60	
Week 12	3.49±2.3	0.60-10.80	

Table (5) percentage improvement in mMASI scores.

percentage of improvement	Response to treatment	Number of patients (%)
< 25	No improvement	5 (14.7%)
25 - 49	Good	8 (23.5%)
50 -74	Very good	16 (47.1%)
75 - 100	excellent	5 (14.7%)

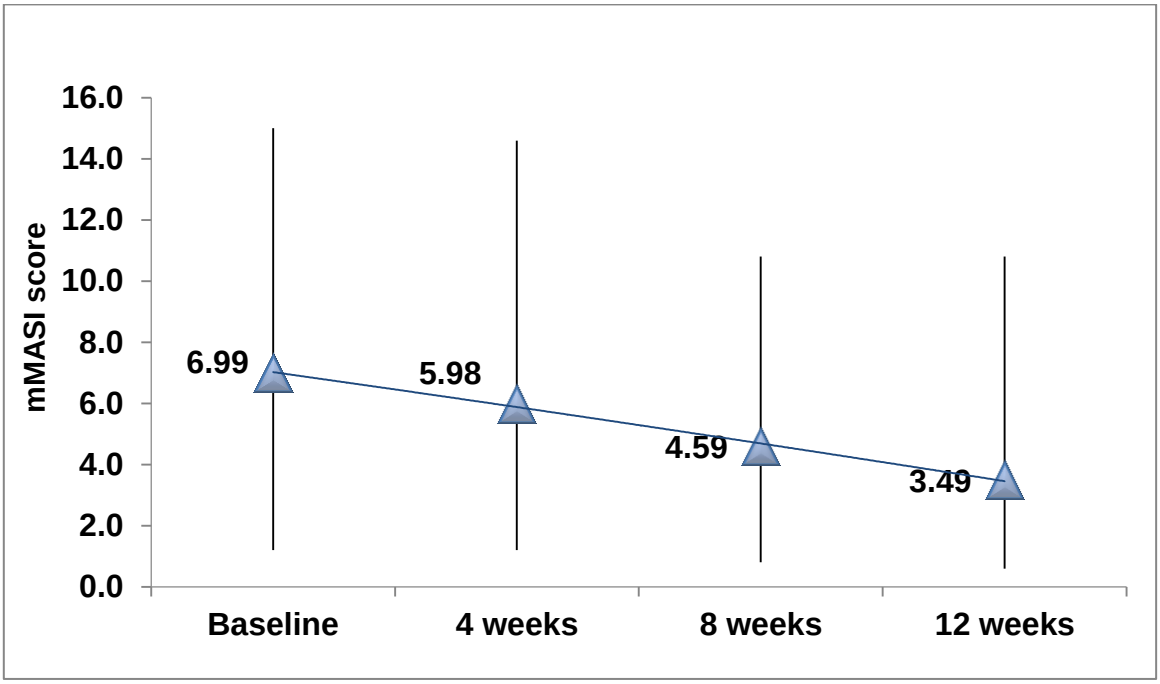


Figure (2) Changes of Modified melasma Area and Severity Index (mMASI) scores with intradermal microinjection of tranexamic acid in 34 patients with melasma.

Discussion

Tranexamic acid TXA had long been used as an antibleeding agent. Latest studies have shown that topical TXA has the ability to prevent Ultraviolet radiation‑induced plasmin activity in keratinocytes leading to a decrease in free arachidonic acid and then prostaglandins production. This leads to decreased tyrosinase activity in the melanocytes. This enzyme is the main enzyme responsible of melanogenesis and by decreasing its activity the melanin contents decreases and then, melasma could be alleviated. Several studies demonstrated that the keratinocytes in human skin secrete the urokinase‑type of plasminogen activator (PA), which promotes melanocytes' activation in vitro. [25] In 2006, Lee *et al.*, conducted the first pilot study on localized TXA intradermal microinjection (4 mg/ml) efficacy. MASI score revealed a statistically significant decrease at the end of the study, which lasted 12 weeks. [23] Our study agrees with their results but the differences are that we used mMASI not MASI to evaluate the melasma severity, and they studied dermal and mixed types of melasma but we studied epidermal and mixed types. Another previous study is Kim *et al.*, (2017) which revealed that oral TXA was more effective than topical form and localized intradermal microinjection of the same drug. With no statistical difference in MASI scores [26]. In our study, we assessed localized intradermal microinjection as a treatment modality of melasma but we did not compare it with oral form of the same drug.

Shetty and Shetty (2018) made a comparison between two groups: (A) with intradermal injection of 4 mg/mL TXA every 3 weeks and (B) with oral 250 mg TXA twice a day. Both groups were treated for 12 weeks. The study revealed that intradermal injection of TXA had 35.6% improvement in MASI score while

oral TXA had 21.7%. [27] We made our sessions every 2 weeks (not 3 weeks) and had 50% improvement in mMASI score at the end of study; we did not study the efficacy of oral TXA in comparison.

In 2019, Pazyar *et al.*, made a comparison between intradermal injected TXA and hydroquinone 4% cream for 12 weeks in the treatment of melasma. It was a split- face controlled clinical trial, they divided 49 patients into two groups, patients received TXA 4mg/ml intradermal injections every 2 weeks on the right side of the face in group A and 10 mg/ml in group B. they treated the left side of the face in both groups with 4% hydroquinone cream. There was significant decrease in MASI scores at the end of the study in all groups without statistically significant difference. comparing between TXA 4mg/ml and hydroquinone 4% cream in group A, MASI score showed significant decreases in week 8 (p=0.02) and week 12 (p=0.02) in hydroquinone sides. There was no significant difference in MASI score between TXA 10 mg/ml and hydroquinone in group B. The higher satisfaction was in group A patients (p=0.001). [15]

In 2019, Patil *et al.*, studied the efficacy of intradermal TXA vs topical TXA vs triple combination (hydroquinone 2%, tretinoin 0.025%, fluocinolone acetonide 0.01%) for the treatment of melasma in 180 patients. MASI score decreased in all three groups but it was statistically significant in Group A (TXA group) that had the least MASI score (decline of 85.71% from baseline to the end of study) followed by triple combination therapy. [4]

Budamakuntla *et al.*, (2013) made a comparison between microneedling and microinjection of 4 mg/ml TXA and concluded that both of them were effective in melasma treating. [24]

In our study, we used intradermal microinjection (mesotherapy) technique to deliver TXA. We assessed the efficacy and safety of TXA in the treatment of epidermal and mixed melasma (we had no dermal melasma patients). The mMASI scores and photographs revealed a significant clinical and statistical improvement in melasma at the end of the study. With more improvement in epidermal type patients than mixed type ones and slightly more improvement in skin type III of Fitzpatrick than skin type IV.

Conclusion.

Localized intradermal microinjection of tranexamic acid at a concentration of 4 mg/ml is an effective and safe therapeutic method for melasma, so that we suggest this procedure.

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