Intradermal injection of tranexamic acid combined with topical hydroquinone cream versus topical hydroquinone cream alone in the treatment of melasma

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Received 15-06-2022 Accepted 16-07-2022

ABSTRACT:

Background: Melasma is a common acquired skin disorder that presents as a bilateral, blotchy, brownish facial pigmentation due to a dysfunction in melanogenesis. It is most common in people who tans easily or have naturally brown skin (Fitzpatrick's skin phototypes III, IV). Although several treatments are currently used, it remains a great challenge.
Aim: This study aims to compare the efficacy of intradermal injection of tranexamic acid (TA) combined with topical hydroquinone cream versus hydroquinone (HQ) cream in the treatment of melasma.
Materials and Methods: In this interventional prospective comparative clinical trial study, 31 patients with facial melasma were divided randomly into 2 groups, A (16 patients) and B (15 patients). Group A received the combination treatment of intralesional tranexamic acid and topical hydroquinone cream, while group B received topical hydroquinone cream alone. Both groups were assessed by MASI score at baseline and weeks 2, 4, 6, and 8.
Results: Thirty-one patients (16 in group A and 15 in group B) completed the study. According to the decline in MASI score, the combination of tranexamic acid and hydroquinone was more effective than hydroquinone alone in the treatment of melasma.
Conclusion: Injection of TA intradermally combined with topical HQ cream can be an effective treatment for melasma.

Keywords: Melasma, Topical hydroquinone, Tranexamic acid, MASI score

الحقن داخل الادمة لحامض الترانيكساميك مع كريم الهيدروكينون الموضعي مقابل كريم العيدروكينون الموضعي وحده في علاج الكلف

الخلاصة:
المدخل: الكلف هو اظطراب جلدي مكتسب شائع يظهر على شكل تصبغ ثنائي، مبقع، بني للوجه بسبب خلل في تكوين الميلانين. وهو اكثر شيوعا لدى الاشخاص الذين يعانون من تسمير البشرة بسهوله، أو لديهم بشرة ذات طبيعة بنية (النماذج الضوئية لجلد فيتزباتريك الثالث والرابع. على الرغم من استخدام العديد من العلاجات حاليا ، الا انه لا يزال يمثل تحديا كبيرا.
الهدف: تهدف هذه الدراسة الى مقارنة فعالية الحقن داخل الادة لحامض الترنيكساميك (TA)مع كريم الهيدروكينون الموضعي مقابل كريم الهيدروكينون (HQ) في علاج الكلف.
المواد وطرائق العمل : في هذه الدراسة التجريبية السريرية المقارنه التداخلية، تم تقسيم 31 مريضا يعنون من الكلف الوجهي بشكل عشوائي الى مجموعتين، مجموعه أ تضم 16 مريضا ، و مجموعه ب تضم 15 مريضا ، تلقت المجموعه (أ) العلاج من حامض الترانيكساميك داخل الافه وكريم موضعي الهيدروكينون، بينما تلقت المجموعه (ب) كريم الهيدروكينون الموضعي لوحده. تم تقيم كلتا المجموعتين من خلال درجة MASI في الاساس والاسابيع 2،4،6, و8.

النتائج : اكمل 31 مريضا (16 في المجموعه أ و 15 في محموعة ب) الدراسة. وفقا لانخفاض في درجة MASI كان الجمع بين حامض الترانيكساميك اكثر فعالية من الهيدروكينون لوحده في علاج الكلف.
الملخص: يمكن أن تكون حقن TA داخل الادمه مع كريم موضعي HQ علاجا فعالا للكلف.

الكلمات المفتاحية : الكلف، الهيدروكينون الموضعي، حامض الترانيكساميك ، قياس درجة الكلف MASI

INTRODUCTION:

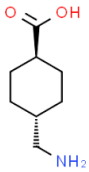
Melasma is a common benign acquired pigmentary dermatosis due to a dysfunction in melanogenesis. It is often found as light to dark-brown patches and macules with irregular borders on the face symmetrically.[1] Adult females are often diagnosed with this disorder, and it is usually seen during pregnancy and hormonal changes in the ovaries.[2] Although the cause and pathogenesis are not clear, the factors like genetic background, pregnancy, oral contraceptive pills, sunlight, ovarian tumors, hormone replacement therapy (HRT), and anticonvulsant drugs and steroids seem to play a role in the onset of this disorder.[3]

One of the standard treatments for melasma is hydroquinone (HQ) cream which is used for several types of skin hyperpigmentation through inhibition of the enzyme tyrosinase. It can also inhibit RNA and DNA synthesis reversibly and affect the production of melanosomes.[4]

Other treatment options include azelaic acid, kojic acid, and ascorbic acid, retinoids, and corticosteroids. Moreover, combination therapies such as hydroquinone and retinoid and corticosteroids are used as the most effective treatments for melasma. Other therapeutic measures, such as chemical peeling and laser, are used for the treatment of resistant melasma.[5-7]

Possible side-effects of these treatments include: erythema, irritation, sensitivity to sunlight, dryness, exogenous ochronosis, desquamation, atrophy, telangiectasia, and hypertrichosis.[7,8]

Lately, tranexamic acid (TA), has been suggested as a new option for the treatment of melasma.[9]



Chemical structure of tranexamic acid

TA can be used to reduce bleeding through inhibition of plasmin and fibrinolysis. So, it inhibits the plasminogen activator which transforms the plasminogen into plasmin. Plasminogen molecule is also found in the basal layer of the human epidermis.[10] The hypopigmentation effect of TA is, therefore, mainly due to its antiplasmin activity.[11]

Additionally, TA can inhibit tyrosinase competitively due to its similarity to tyrosine in a portion of its structure.[12] Histological examination showed that TA has an important role in the reduction of vascularity and erythema as well as the number of mast cells in the dermis because plasmin transforms the vascular endothelial growth factor (VEGF) into a diffusing form.[13,14] TA is used orally, topically, and as microinjection for the treatment of melasma and the amount used to treat melasma is much less than that required for its antifibrinolytic effects.[15]

PATIENTS AND METHODS:

Aim of the study: To compare the efficacy of intradermally injected tranexamic acid with topical hydroquinone cream versus hydroquinone cream alone in the treatment of melasma.

Study design: To achieve the aim of the present study, An Interventional prospective comparative clinical trial study was conducted at Erbil Dermatology Teaching Centre (EDTC) between May 2021 to May 2022.

Inclusion criteria

1. Adults (age≥18 years).
2. Cases of melasma.

Exclusion criteria

1. Younger age (age<18 years).
2. Pregnancy.
3. Lactation.
4. Melasma treatment 1 month before the study.
5. Take oral contraceptive pills or any phototoxic drug within 1 month prior to study.
6. Patients refused to participate in the study.

Sample size & Sampling:

A sample of 31 patients was enrolled in the the study and randomly divided into 2 groups (A and B). Group A received sessions of intradermal injection of tranexamic acid (TA) on the melasma site every 2 weeks for a total of 4 sessions plus application of topical 4% hydroquinone (HQ) cream every night. During the sessions, 500mg/5ml vial of TA was used. The injections were done using an insulin syringe (30 Gauge needle, 4mm) with a dilution of the TA, prepared by adding 4 units of TA to the syringe with the remaining filled with normal saline (=4mg=0.04ml). Each patient received a total of 3-6 ml/session of the diluted TA with a 1 cm interval between the injection sites. However, group B patients applied only the topical 4% HQ cream every night. Both groups were asked to use a sunscreen of SPF 50 during the treatment period. The total duration of treatment for both groups was 8 weeks with a follow-up every 2 weeks for each patient.

The patients were evaluated before and after treatment by these parameters: Photographs, MASI score (Melasma And Severity Index) (as shown in **Appendix I**), and patient satisfaction using a four scale grading; poor: response rate=0-25%, fair: response rate=25-50%, good: response rate=50-75%, excellent: response rate=75-100%.

Data collection: The main sources of data were obtained directly from grouped patients by researcher interviewing them, using a specially prepared questionnaire as shown in (**Appendix II**). Each patient enrolled in this study was coded by number.

Ethical Consideration

To conduct the study, informed verbal consent will be obtained from the patients with melasma to participate in this study. The purpose of the study will be carefully explained to each participant, and anonymity for each participant will be kept confidential.

*** Information sheet:** (as shown in **Appendix III**)

*** Consent Form:** (as shown in **Appendix IV**)

RESULTS:

This study included thirty-one patients with melasma divided into two study groups (16 patients treated by HQ & TA and 15 patients treated by HQ alone). No significant differences were observed between both study groups regarding age (p=0.78), gender (p=0.57), residence (p=0.58), occupation (p=0.24) and marital status (p=0.06). (***Table 1***)

Table 1: Distribution of patients' general characteristics according to study groups.

Variable	Study groups				P
	HQ&TA		HQ		
	No.	%	No.	%	
Age					0.78 NS
<30 years	3	18.8	4	26.7	
30-39 years	11	68.8	10	66.7	
≥40 years	2	12.5	1	6.7	
Gender					0.57 NS
Male	2	12.5	3	20.0	
Female	14	87.5	12	80.0	
Residence					0.58 NS
Urban	14	87.5	14	93.3	
Rural	2	12.5	1	6.7	
Occupation					0.24 NS
Student	0	-	1	6.7	
Government employee	2	12.5	0	-	
Private employee	1	6.3	3	20.0	
Unemployed	13	81.3	11	73.3	
Marital status					0.06 NS
Single	0	-	3	20.0	
Married	16	100.0	12	80.0	

NS=Not significant.

No significant differences were observed between both study groups regarding the family history (p=0.6), disease duration (p=0.1), skin types (p=0.8), affected Centro facial area (p=0.9), affected malar area (p=0.9), and affected mandibular area (p=0.9). (***Table 2***).

Table 2: Distribution of clinical characteristics according to study groups.

Variable	Study groups				P
	HQ&TA		HQ		
	No.	%	No.	%	
Family history					0.6 NS
Positive	6	37.5	7	46.7	
Negative	10	62.5	8	53.3	

Disease duration					0.1 NS
<5 years	12	75.0	7	46.7	
≥5 years	4	25.0	8	53.3	
Skin types					0.8 NS
Type 2	3	18.8	3	20.0	
Type 3	11	68.8	11	73.3	
Type 4	2	12.5	1	6.7	
Affected centrofacial area					0.9 NS
Positive	11	68.8	10	66.7	
Negative	5	31.3	5	33.3	
Affected malar area					0.9 NS
Positive	13	81.3	12	80.0	
Negative	3	18.8	3	20.0	
Affected mandibular area					0.9 NS
Positive	2	12.5	2	13.3	
Negative	14	87.5	13	86.7	

NS=Not significant.

The mean MASI score of melasma was significantly reduced after 8 weeks of treatment with tranexamic acid with topical hydroquinone (p<0.001). The mean MASI score of melasma was significantly reduced after 8 weeks of treatment with topical hydroquinone alone (p<0.001). (***Table 3***).

Table 3: MASI scores outcome according to study periods.

Variable	**Study periods**					**P**
	Baseline	**2nd week**	**4th week**	**6th week**	**8th week**	
HQ&TA						
MASI score	11.8±3.6	10±3.5	9±3.1	7.7±3.1	7.5±3.2	**<0.001** S
HQ						
MASI score	6.3±3.5	6±3.2	5.4±2.8	5.2±2.5	5.2±2.5	**<0.001** S

S=Significant.

The mean MASI score of melasma at baseline was significantly higher among patients treated with tranexamic acid with topical hydroquinone (p<0.001). The mean MASI score of melasma at the 8th week was significantly higher among patients treated with tranexamic acid with topical hydroquinone (p<0.001). The mean decline in MASI score after 8 weeks of treatment for melasma was significantly higher among patients treated with tranexamic acid with topical hydroquinone (Figure 1) (p=0.001). (***Table 4***)

Table 4: MASI scores outcome according to study groups.

MASI score	Study groups		P
	HQ&TA Mean±SD	HQ Mean±SD	
Baseline	11.8±3.6	6.3±3.5	**<0.001** S
8th week	7.5±3.2	5.2±2.5	**0.04** S
Decline	4.3±3	1±1.5	**0.001** S

S=Significant.

No significant differences were observed between both study groups regarding patient satisfaction (p=0.52) and affected adverse effects (p=0.86). Only three patients treated by HQ & TA had adverse effects (two patients developed redness and one patient developed irritation), while two patients treated by HQ alone had adverse effects (one patient developed redness and one patient developed irritation). (***Table 5***)

Table 5: Distribution of satisfaction and adverse effects according to study groups.

Variable	Study groups				P
	HQ&TA		HQ		
	No.	%	No.	%	
Patient's satisfaction					0.52 NS
Poor	3	18.8	5	33.3	
Fair	6	37.5	7	46.7	
Good	4	25.0	2	13.3	
Excellent	3	18.8	1	6.7	
Adverse effects					0.86 NS
No adverse effect	13	81.3	13	86.7	
Redness	2	12.5	1	6.7	
Irritation	1	6.3	1	6.7	

NS=Not significant.

DISCUSSION:

Melasma is a prevalent benign acquired skin disease presented with hyperpigmented macules or patches mostly on the face. It causes cosmetic problems associated with psychosocial effects.[16]

The current study found no significant differences in age and gender between patients treated by HQ & TA and patients treated by HQ alone. However, the most studied patients of both groups were women in the reproductive age group. This

finding is similar to the results of Sharquie et al[17] study in Iraq which reported that melasma in Iraq is a common dermatosis affecting reproductive age women with a history of sun exposure. Most of the studied melasma cases in our study were urban residents with no significant difference in residence between both study groups. Similarly, Deshpande et al[18] cross-sectional study in India revealed that melasma is more prevalent in urban resident patients. In our study, most of the studied melasma cases were unemployed with no significant difference in occupation between both study groups. Leeyaphan et al[19] cross-sectional study in Thailand reported that a poorly income population is more likely to be affected by melasma. Our study showed that most of the studied melasma cases were married with no significant difference in marital status between both study groups. This finding coincides with the results of Handel et al[20] study in Brazil.

Although our study showed no significant differences between both study groups regarding family history, disease duration, skin types, affected centrofacial area, affected malar area, and affected mandibular area, the family history of melasma represented a high proportion of melasma cases. Consistently, Achar et al[21] studies in India stated that positive family history of melasma was present in 33.3% of melasma cases. The most prevalent skin type in both study groups was type III. This finding is consistent with the results of Sharquie et al[17] study in Iraq. The malar and centrofacial areas are common areas affected by melasma in the current study. These findings are in agreement with the results of Raju et al[22] study in India. Our study showed no significant difference in general and clinical characteristics between both study groups. These findings are similar to the results of Pazyar et al[3] prospective controlled clinical trial study in Iran which found high effectiveness of intradermal injected tranexamic acid as compared to hydroquinone cream in the treatment of melasma with no significant differences in general and clinical characteristics between both studies groups.

The present study showed that the mean MASI score of melasma was significantly reduced after 8 weeks treatment with tranexamic acid with topical hydroquinone ($p<0.001$). This finding is similar to the results of Al-Hamamy and Aziz interventional single-blinded comparative outpatient study[23] in Iraq on 32 patients with melasma which reported a significant decline in MASI score of patients treated with intradermal injection of tranexamic acid with topical hydroquinone 4%. Our study revealed that the mean MASI score of melasma was significantly reduced after 8 weeks of treatment with topical hydroquinone alone ($p<0.001$). This finding is parallel to the results of Hamadi et al[24] study in Iraq which reported a significant effect of topical hydroquinone in declining MASI scores of patients with melasma after 8-weeks treatment duration.

The present study found that the mean decline in MASI score after 8 weeks of treatment for melasma was significantly higher among patients treated with tranexamic acid with topical hydroquinone ($p=0.001$). This finding is similar to the results of Tehranchinia et al[25] studies in Iran on 55 patients with melasma, each side of the face was either treated with tranexamic acid with topical hydroquinone or by topical hydroquinone alone and found that MASI score was declined in both study groups, but with a higher decline in face side treated by tranexamic acid with topical hydroquinone. Tranexamic acid (TA) is an anti-fibrinolytic drug being highly applied for different dermatological disorders recently. The tranexamic acid is showing higher efficacy in managing melasma, post-inflammatory hyperpigmentation, urticaria, angioedema and homeostasis.[26]

A recent study conducted in Thailand by Lueangarun et al[27] reported that intradermal injection of 4 mg/ml for melasma patients showed a significant decline in MASI score for the 16 weeks. However, melasma recurrence was observed in 48 weeks follow-up after treatment[27].

The current study showed no significant differences between both study groups regarding affected adverse effects (p=0.86), however, 3 patients treated by HQ & TA had adverse effects (2 patients developed redness and 1 patient developed irritation), while 2 patients treated by HQ alone had adverse effects (1 patient developed redness and 1 patient developed irritation). These findings are in agreement with the results of the Tehranchinia et al[25] studies in Iran. Our study showed no significant differences observed between both study groups regarding patient satisfaction (p=0.52). This finding is parallel to the results of Pazyar et al[3] prospective controlled clinical trial study in Iran which showed no statistically significant difference in satisfaction between patients treated with intradermal tranexamic acid with topical hydroquinone or by topical hydroquinone alone, however, the satisfaction was significantly obvious with increasing dose of tranexamic acid.

CONCLUSION:

According to the decline in MASI score, the intradermal injection of tranexamic acid combined with topical hydroquinone has higher efficacy than topical hydroquinone alone in the treatment of melasma. The safety and patient satisfaction of both treatment types is equal. Therefore, this study recommends that dermatologists add tranexamic acid to conventional hydroquinone cream in the treatment of melasma.

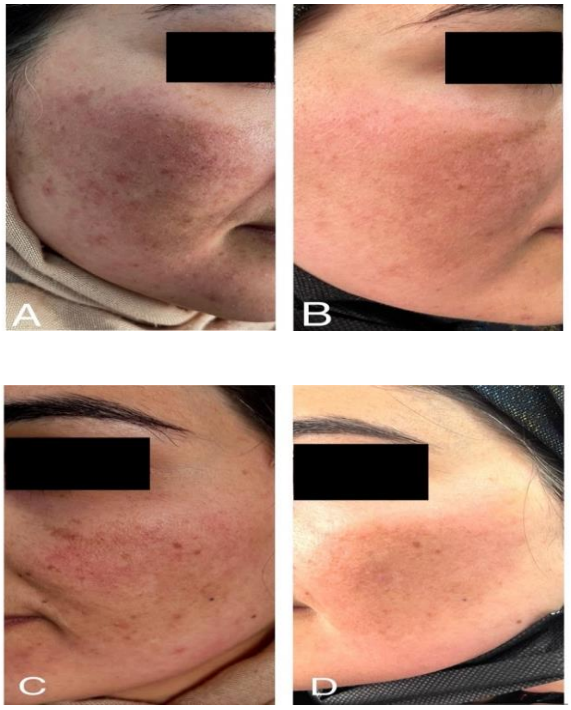


Figure 1 Right cheek before treatment (A), after treatment with intradermal TA+HQ (B) Left cheek before treatment (B), after treatment with intradermal TA+HQ (D)

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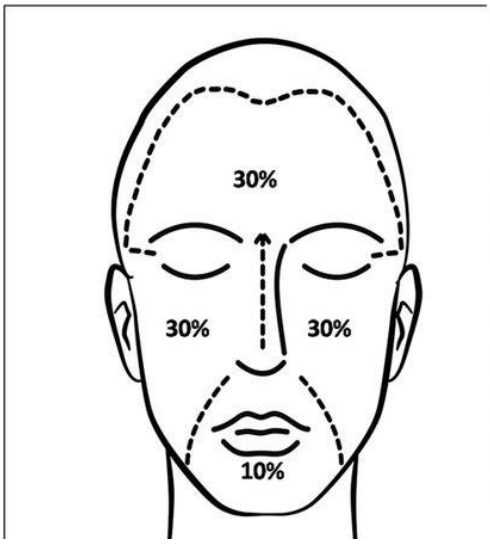
Appendix I
MASI score



1. MASI score is calculated by dividing the face into four areas; and each area is weighted such that the forehead (F), right malar area (MR), and left malar area (ML) are 30% each, and the chin (C) is 10%.
2. Amount of pigmentation involved by melasma in these four areas (F, MR, ML, and C) is graded as a numerical value:
   - 0 = no involvement
   - 1=less than 10% involvement
   - 2=10–29% involvement
   - 3 = 30–49% involvement
   - 4=50–69% involvement
   - 5=70–89% involvement
   - 6=90–100% involvement
3. Severity of melasma is graded upon two factors; darkness (D) of melasma compared to the normal skin and homogeneity (H) of hyperpigmentation on a scale from 0 to 4: The rating scale for both darkness and homogeneity of melasma is:
   - 0 = absent
   - 1 = slight
   - 2 = mild
   - 3= marked
   - 4 = maximum

Appendix II
Questionnaire

Intradermal injection of tranexamic acid combined with topical hydroquinone cream versus topical hydroquinone cream alone in the treatment of melasma

Name of patient: ……
Code of patient: ……
Age of patient: ……
Tel Number: ……..
Gender : ☐ Male ☐ Female

Residency: ☐ Urban ☐ Rural

Occupation: ☐ Student ☐ Government Employee

☐ Private Employee ☐ Unemployed ☐ Retired

Marital Status: ☐ Single ☐ Married ☐ Divorced
Family history of Melasma: ☐ Yes ☐ No
Duration of disease in months: ……
Fitzpatrick's skin type: ☐ Type I ☐ Type II ☐ Type III
☐ Type IV ☐ Type V ☐ Type VI
Area affected: ☐ Centrofacial ☐ Malar ☐ Mandibular
Baseline MASI Score …….

MASI Score in 2nd week ……

MASI Score in 4th week …….

MASI Score in 6th week …….

MASI Score in 8th week …….

Patient satisfaction score: ☐ Poor ☐ Fair ☐ Good ☐ Excellent

Adverse effects of treatment: ☐ Redness ☐ Peeling ☐ Hypopigmentation
☐ Irritation ☐ No adverse effect

Appendix III
Information sheet
I am Lavan Yaseen Taha, Senior House Officer of Dermatology. I have a research on intradermal injection of tranexamic acid combined with topical hydroquinone cream versus topical hydroquinone cream alone in the treatment of melasma in Erbil Dermal Teaching Centre. I shall provide this drug for free for you.

Appendix IV
Consent Form

Department of Dermatology
Intradermal injection of tranexamic acid combined with topical hydroquinone cream versus topical hydroquinone cream alone in the treatment of melasma

I confirm that I have read and understand the information about the project as provided in the participant information sheet dated in / / 2021.
I confirm that I have had the opportunity to ask questions and the researcher has answered any questions about the study to my satisfaction.
I understand that my participation is voluntary and that I am free to withdraw from the project at any time without having to give a reason and without any consequences.
I understand that I can withdraw my data from the study at any time.

Name:
Signature