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Original Article

The effectiveness of intradermal injection and topical tranexamic acid in melasma

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Abstract

Abstract Melasma is a hyperpigmentation disorder caused by the hyperactivity of epidermal melanocytes in the facial area that is very common in Asian races. Tranexamic acid is a fibrinolytic agent that has antiplasmin properties and is shown to be safe in preventing pigmentation. This study elucidates the effectiveness of intradermal injection compared with topical tranexamic acid (TA) in melasma.

Methods The research subjects were separated into two groups: intradermal tranexamic acid injections every four weeks for eight weeks and topical tranexamic acid given by compressed dressing every two weeks for eight weeks. MASI score and melanin index were measured at the beginning and end of the study.

Results Eighteen patients (56%) received an intradermal tranexamic acid injection, and 14 patients (44%) received topical tranexamic acid. There were significant mean differences in melanin index and MASI score before and after treatment between the topical and injection TA groups ($p < 0.05$).

Conclusion TA injection is more effective in reducing MASI scores and melanin index compared to topical TA in the treatment of melasma, with longer treatment intervals and lower cost.

Key words
Tranexamic acid injection; Topical tranexamic acid; Melasma; Hyperpigmentation; MASI.

Introduction

Melasma is a hyperpigmentation disorder that is very common in Asian races and is characterized by symmetrical light to dark-brown patches. The disease is caused by hyperactivity of epidermal melanocytes in different areas of the face, especially on the forehead, malar area and chin.[1,2] Ninety percent of melasma cases are reported in women during reproductive age with Fitzpatrick skin type III to V. Pathophysiological factors include sun exposure, genetic susceptibility, hormone therapy, pregnancy, cosmetics and photosensitization by certain drugs.[3,4]

Various treatment modalities are used to treat melasma, such as topical agents (hydroquinone, ascorbic acid, azelaic acid, etc.) and broad-spectrum sunscreens, chemical peels and LASERs.[5] Tranexamic acid (TA) is a synthetic analog of the amino acid lysine that inhibits melanin synthesis by interfering with the keratinocyte-melanocyte interaction.[6,7] The route of administration of TA in case of hyperpigmentation can be orally, topically, intradermal injection and *micro-needling*.[8,9] This study was conducted to compare the efficacy of

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intradermal TA injections once every 4 weeks and topical TA administration with compressed dressing every 2 weeks for 8 weeks.

Methods:

We conducted a case control study (perspective randomized open label trial) on females with melasma. The investigation was conducted under the Helsinki Declaration on Human Experiments of the World Medical Association. This study was approved by the ethics committee of the Faculty of Medicine, Universitas Gadjah Mada.

The study included 32 females with melasma who had never received any treatment for at least two weeks before the study. The exclusion criteria are patients in pregnancy and lactation, on other medication treatments such as hormonal contraception, steroids, nonsteroid anti-inflammation drugs, topical treatment for melasma during the last month, known allergies to TA, coagulation, and thrombotic disorders.

The Melasma Area Scoring Index (MASI) and melanin index measurement, which were determined after a thorough dermatological examination (including skin photo type, melasma location, clinical type utilizing the wood's lamp, and photographic assessment), were completed. All included patients will be randomly assigned based on the number allocation method into 2 groups: the tranexamic acid injection group (group A) and the compressed dressing tranexamic acid group (group B).

Group A patients received intradermal TA injections (100 mg/mL) with an insulin syringe, diluted by 0.4cc NaCl 0.9%, to obtain a TA concentration of 20mg/mL. Then 0.2-0.4mL of solution was injected intradermally, leaving 1 cm between injection sites. The sessions were repeated every four weeks for eight weeks. The group B patients received topical TA with a compressed dressing, followed by 10 minutes of radiofrequency procedures every two weeks for eight months. All patients were instructed to avoid as much sun exposure as possible and to avoid using any topical preparations except sunscreen with a sun protection factor of 50 in the morning, with instructions to apply a standard amount of sunscreen and reapply it every 2-3 hours. The melanin index measurement and the MASI score were used to assess progress at the beginning and end of the treatment period.

Results

This study included 32 female melasma patients ranging in age from 18 to 50 years with a mean and SD of 32.78±7.90 years. The patients had Fitzpatrick skin types of 3 and 4. The most common predisposing factor was sun exposure history followed by a family history of melasma. Characteristics of all patients are illustrated in **Table 1**.

Efficacy assessment Total of 32 participants with 18 patients (56%) who got intradermal tranexamic acid injection and 14 patients (44%) with topical tranexamic acid. There was a decrease in the mean value of melanin index in

Table 1 Baseline characteristics of all melasma patients (n=32).

	n (%)
Age (years)	
Mean ± SD	32.78 ± 7.90
Range	18 - 50
Predisposing factors	
None	11 (34,37)
Hormonal contraception	0
Pregnancy	0
Family history	17 (53,12)
Sun exposure	29 (90,62)
Skin phototype	
III	9 (28,12)
IV	23 (71,87)

Table 2 MASI score before and after treatment in injection and topical TA groups.

MASI Score	*Injection group (n=18)*	*Topical group (n=14)*	*P-value*
Before treatment Mean± SD	12.8 ± 5.5	7.3 ± 5.5	<0.05
After treatment Mean± SD	7.2 ± 3.5	3.9 ± 3.6	<0.05
P-value	<0.05	<0.05	

Table 3 Melanin index before and after treatment in injection and topical TA groups.

Melanin Index	*Injection group (n=18)*	*Topical group (n=14)*	*P-value*
Before treatment Mean± SD	59±3.8	54.4±6.1	<0.05
After treatment Mean± SD	53.6±2.9	50.7±3.9	<0.05
P-value	<0.05	<0.05	

the topical TA group before and after sequential treatment was (54.4±6.1) and (50.7±3.9), ($p<0.05$). There was a decrease in the mean melanin index in the injection TA group before and after sequential treatment (59±3.8) and (53.6±2.9), ($p<0.05$).

There was a decrease in the MASI score in the topical TA group before and after sequential treatment (7.3±5.5) and (3.9±3.6), ($p<0.05$). While the MASI score value **(Table 2)** in the injection TA group before and after sequential treatment was (12.8±5.5) and (7.2±3.5), ($p<0.05$). There were significant differences in the melanin index **(Table 3)** before and after treatment between the topical and injection TA groups respectively (53.7±3.1) and (37.2±3.1), ($p<0.05$). There were significant differences in mean MASI scores before and after treatment between groups respectively (5.7±3) and (3.4±2.3), ($p<0.05$).

Discussion

Melasma is a skin disorder with hyperpigmented macular manifestations on the face that are symmetrical.[8,10] Previous studies have suggested that melasma causes cosmetic problems and caused psychosocial distress. Melasma treatment modalities include the use of sunscreen, hydroquinone, Kligman formula, and laser.[8,9]

Tranexamic acid has anti-plasmin activity with anti-melanogenic and angiogenic potential. Previous studies revealed that intradermal TA injection is an effective and safe method.[11] Recent studies have found that the diameter and amount of vascularity as well as VEGF expression in melasma lesions are increasing, thereby suggesting that TA can improve melasma clinically through two such mechanisms.[12]

Hydroquinone is the gold standard for melasma therapy. However, this topical whitening agent can cause exogenous ochronosis.[11] Other treatments include tretinoin, kojik acid, glycolic acid, and ascorbic acid. All of these topical treatments produce minimal to moderate pigment resolution in approximately 60% of patients but are reported to irritate the skin, create post-inflammatory hyperpigmentation, and take a rather long time to achieve skin brightening, thereby reducing patient satisfaction. Topical treatments usually do not give a good effect on dermal and mixed melasma.[13]

Our findings indicate that topical and intradermal injections of TA lead to significant improvement in melasma by decreasing the MASI score and melanin index. A study similar to ours revealed a decrease in the average MASI score of 4.2 (31.8%) in week 8 and 5.65 (42.74%) in week 12. 86% of the participants in the study rated the treatment's efficacy and degree of pigmentation improvement as moderate to good.[14] The same results were obtained in a study by Budamakuntla *et.al*, (2013). with an improvement of 35.72%, the average MASI score from the beginning of the

study was (6.93±2.16) and at the end of the study was (4.45±1.69), (*p<0.01*).[15] Another study of 30 participants with single therapy of compressed dressing topical TA (5 mL) revealed improvements in MASI of 49.6% at the 12th week of the study. The TA compressed dressing was given three times a week for three months.[2]

This study revealed significant differences in MASI scores and melanin index between the intradermal and topical TA injection groups due to the localized micro-injection or called "*mesotherapy"* is an intradermal or subcutaneous micro-injection of 0.05 to 0.1 ml of the drug on the site of the body that has medical or aesthetic problems.[1,16] This method allows giving a sufficient amount of the drug directly to the lesion area. Drug administration with the *mesotherapy* method avoids the restriction of the amount of the drug by the stratum corneum which occurs in topical drugs. In addition, mesotherapy allows lower drug dosage administration.[14,17]

Considering adverse effects, all patients reported no cutaneous or systemic side effects with the use of TA, except for moderate discomfort during injection in the TA injection group and slight irritation with the use of TA cream. This was supported by the majority of investigations.[10,18]

Conclusions

In the treatment of melasma, TA injection is more effective than topical TA in decreasing MASI scores and melanin index, with longer treatment intervals and relatively low cost.

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