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Original Study

Melasma A Cosmetic Bane and Intradermal Tranexemic Acid an Effective Rescue Option

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Abstract

Background: *Melasma is a common, acquired pigmentary disorder among Asians that occurs in sun-exposed areas mostly involving the face predominantly the malar areas of cheek. Though the exact etiology is not known various factors have been implicated in the etiopathogenesis.*

Aim and Objective: *To assess the therapeutic efficacy and safety of intradermal tranexamic acid microinjections.*

Materials and Methods: *Retrospective analysis of 50 consecutive patients with melasma was done who received 3 doses (at 0, 4 and 8 weeks) of tranexamic acid intradermal microinjections every 4 weeks. Improvement was accessed by Melasma Assessment Severity Index (MASI) score at the end of 4, 8 and 12 weeks of starting the treatment.*

Results: *A total of 5o patients were retrospectively analysed. Among these 41 patients who completed the study 37 (90%) were females and 4 (9.7%) were males in age group of 18 -55 years. All 41 patients showed significant decrease in mean MASI score with intradermal infiltration of TXA microinjections at week 4, 8 and 12 when compared with baseline MASI scores that are from 11.29±6.07 to 2.37±1.75. Transient oedema and pain at the injection site were the only reported adverse effects.*

Conclusion: *In our study, Intradermal TXA microinjections were found effective and safe in the treatment of melasma with a significant reduction in MASI score.*

Introduction

Melasma (Greek '*melas*'- black) is a common, acquired pigmentary disorder among Asians that occurs in sun-exposed areas mostly involving the face predominantly the malar areas of cheek, it may also appear on forehead, chin, nose, upper lips and temple.[1] The term 'chloasma' (Greek '*chloazein*'- to be green) was often used to describe melasma developing during pregnancy.[2] Melasma presents as slowly enlarging, symmetrical tan to brown macules or patches with well-defined geographic borders. It is found in all racial groups but is more common in subjects with darker skin. Multiple factors have been implicated in the etiopathogenesis of melasma which includes exposure to ultraviolet (UV) radiation,

pregnancy, contraceptive pills, hormone replacement therapy, cosmetics, phototoxic and antiseizure medications.[3] Serum plasminogen activator (PA),[4] which is known to activate melanogenesis has been shown to increase with the use of oral contraceptives. Although, no specific gene has been identified in the pathogenesis of melasma, familial occurrence and the higher prevalence of the disease among Hispanics and Asians[5] suggests genetic predisposition. On histopathology, an increase in the number of functionally altered melanocytes is found in the epidermis of patients with melasma..[6] Three distinct clinical patterns recognized are centrofacial, malar and mandibular. Traditionally, melasma has been classified into four distinct types according to the fluorescence of the macules under Wood's light and the histological location and depth of the pigment[7] namely epidermal type, dermal type, mixed and intermediate type. Melasma is difficult to treat particularly in dark skin individuals thus various treatment options aim by either inhibiting melanocyte activity, inhibiting melanin synthesis, removing melanin, and disrupting the melanin granules contained within melanosomes.[8] Various treatment modalities which are used include hydroquinone, alone or in combination with tretinoin[9] and a corticosteroid. The original triple combination formula was developed by Kligman and Willis[10] in 1975 and consisted of hydroquinone (HQ) 5%, tretinoin 0.1% and dexamethasone (0.1%) and had been widely used. Other modalities include retinoic acid, kojic acid, azelaic acid, and peeling agents like glycolic acid, trichloroacetic acid, salicylic acid, and lactic acid. Physical agents like lasers which includes pulsed carbon dioxide laser, Q-switched ruby laser, Q-switched Alexandrite laser, erbium:yttrium-aluminum-garnet (Er:YAG) laser and intense pulsed light (IPL)[11-15] and dermabrasion have all been tried with limited success.[9,10] Despite the multiplicity of therapies, no specific therapy is universally effective and their efficacy and safety remains controversial. Tranexamic acid (Trans-4-Aminomethylcyclo-hexanecarboxylic acid), an antifibrinolytic agent, a plasmin inhibitor, recently has been demonstrated to inhibit plasminogen-keratinocyte interaction. Plasminogen exists in human epidermal basal cells and the cultured human keratinocytes produce plasminogen activator (PA) and these may themselves activate melanocytes[16, 17]thus justifying its usage in treatment of melasma. Tranexamic acid apparently can prevent the activation of melanocyte by sunlight, hormonal influence, and injured keratinocyte. Thus, it not only reduces the formation of melasma but is also likely to prevent recurrences. TXA is routinely used as hemostatic agent to prevent abnormal fibrinolysis and reduce blood loss in high risk surgeries such as cardiac, liver, vascular, large orthopaedic procedures and menstrual bleeding.[4] The recommended oral dose of TXA for clinical use as antifibrinolytic is 0.5–1.5 g three times daily. Its usage in the treatment of melasma was first reported in 1979 by Nijor.[18] Sadako[19] incidentally observed beneficial effect of TXA in melasma while treating a patient with chronic urticaria. TXA, as a skin lightening agent, can be used orally, as topical in liposome formulations, intravenously, or transepidermally by microinjection or microneedling.[20,17] Common side effects include nausea, vomiting and diarrhea while with higher doses thromboembolism, pulmonary embolism and myocardial infarction have been reported. It is contraindicated in patients with acquired defective color vision, active coagulopathies and known hypersensitivity to TXA. Micro needle technology offers a minimally invasive and painless route of drug delivery.[21] In view of the large number of cases of melasma at high altitude and paucity of data from our region on efficacy and safety of TXA in melasma a retrospective analysis was done.

Aims and Objectives

In patients of melasma, to assess the therapeutic efficacy and safety of local infiltration of tranexamic acid microinjections.

Material and Methods

Retrospective analysis of 50 consecutive patients with melasma who were started on treatment with tranexamic acid intradermal microinjections in the outdoor clinic of Dermatology at Civil Hospital, Theog between Aug 18 and March 2019 was done.

Exclusion criteria

- Pregnant and lactating women.
- Patients who took any other melasma therapy within last 6 months.
- Patients taking oral contraceptives or on HRT.
- Patients with history of thromboembolism, bleeding disorders, and abnormal coagulation profile.
- Patients with psychological disorders.

History and Clinical examination

- Detailed history regarding age, sex, occupation, onset, duration and progression of Melasma, aggravating factors, use of medications were recorded.
- Various Clinical patterns of Melasma were noted (Table- 1).

Table-1: Clinical patterns of Melasma

Clinical patterns of Melasma
1. Centrofacial
2. Malar
3. Mandibular

- Laboratory tests including platelet counts, bleeding time, clotting time and prothrombin index (International normalized ratio, INR) at baseline and at completion of treatment (12 weeks) was done.

Patient evaluation

Improvement was accessed by Melasma Assessment Severity Index (MASI) score at the end of 4, 8 and 12 weeks of starting the treatment and was graded as shown in Table-2. MASI scores were calculated using the original method by Kimbrough-Green et al.[22]

Table-2: Improvement by reduction in MASI Score

Grades of improvement	Reduction in MASI Score
1. No response	no improvement
2. Mild response	<25% improvement
3. Moderate response	25% to < 50% improvement
4. Good response	50% to < 75%improvement
5. Very good response	>75% improvement

Treatment (drug dose and duration)

Tranexamic acid (TXA) is available in a packing of 500 mg/5mL vial. Intradermal microinjection was prepared by taking about 0.04 ml (4 units) of TXA in a 100 units/ml insulin syringe and was diluted with normal saline up to 1 ml (100 units) to get a concentration of 4 mg/ml of TXA. After gently cleaning the melasma affected area with normal saline, topical EMLA cream was applied and left for 45 to 60 min prior to intradermal TXA injections for surface anesthesia. Melasma lesions were infiltrated with multiple microinjections of TXA (4mg/ml) intradermally given at a gap of 1cm at every 4 weeks (0, 4 and 8 weeks) for a total of 3 cycles to a maximum infiltrated dose of 8 mg per cycle depending on the extent of involvement. Improvement was documented of all patients at every visit (every 4 weeks) along with the side effects known to be associated with TXA. Patients were advised to apply sunscreen every 4 hours during the day while on treatment.

Results

Retrospective analysis of 50 consecutive patients with melasma who were started on treatment with intradermal tranexamic acid microinjection during Aug 2018 to March 2019 was done and various parameters before and after treatment were analysed.

Demographic and Disease profile

There were 50 patients (M:F 5:45) who received intradermal TXA microinjections having the clinical disease for duration of 5 months to 22 years (Table-3) with a mean duration of 5.05 ± 4.76 years and a mean MASI score of 11.33 ± 6.45.

Table-3: Demographic and Disease profile

Characteristics		**(*n* =50)**
No. of patients (Female + Male)		50 (45 +5)
Age	Range (years)	18 – 55
	Mean ± SD (years)	35.56 ± 8.94
Duration of Melasma	Range (Years)	0.5 – 22
	Mean ± SD (years)	5.05 ± 4.76
MASI Score	Range	3.0 – 30.4
	Mean ± SD	11.33 ± 6.45

Clinical patterns

Centrofacial pattern was seen in majority 29(70%) of the patients and 12(29%) patients presented with malar pattern. (Figure 1,2,3)

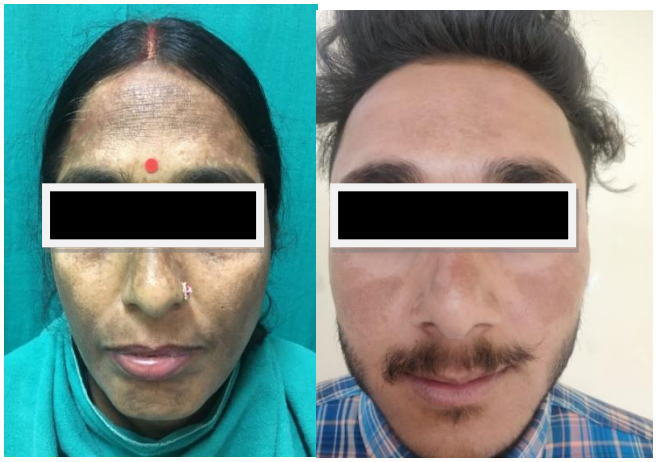

Figure 1 and 2: Centrofacial pattern

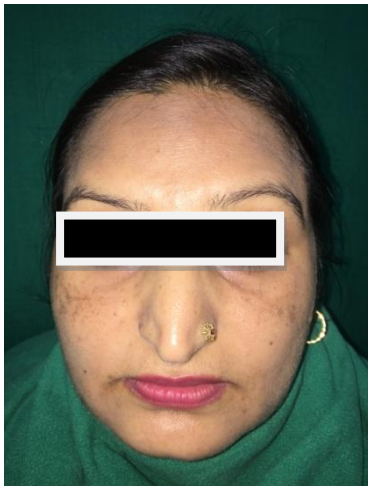

Figure 3: Malar pattern of melasma

Response to treatment

Nine patients dropped out at various stages of the follow up. Among 41 patients who completed the study 37 (90%) were females and 4 (9.7%) were males in age group of 18 -55 years having a mean MASI score of 11.29 ± 6.07 at baseline (Table-4). All 41 patients showed significant decrease in mean MASI score with intradermal infiltration of TXA microinjections at week 4, 8 and 12 when compared with baseline MASI scores that are from 11.29±6.07 to 2.37±1.75 (Table-4) (Figure 4,5).

Table-4: Mean reduction in MASI scores of patients who completed the study

Follow up	**(*n* = 41)**
Baseline MASI Score	11.29±6.07
At 4 weeks	9.34±5.62
At 8 weeks	5.80±4.55
At 12 weeks	2.37±1.75

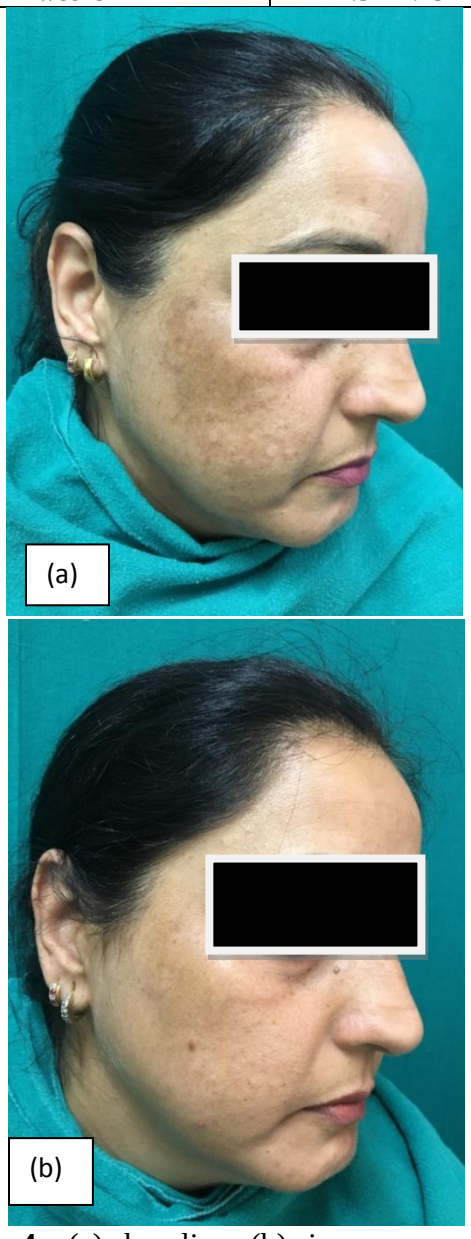

Figure 4: (a) baseline (b) improvement after receiving 3 doses of intradermal tranexamic acid at week 12.

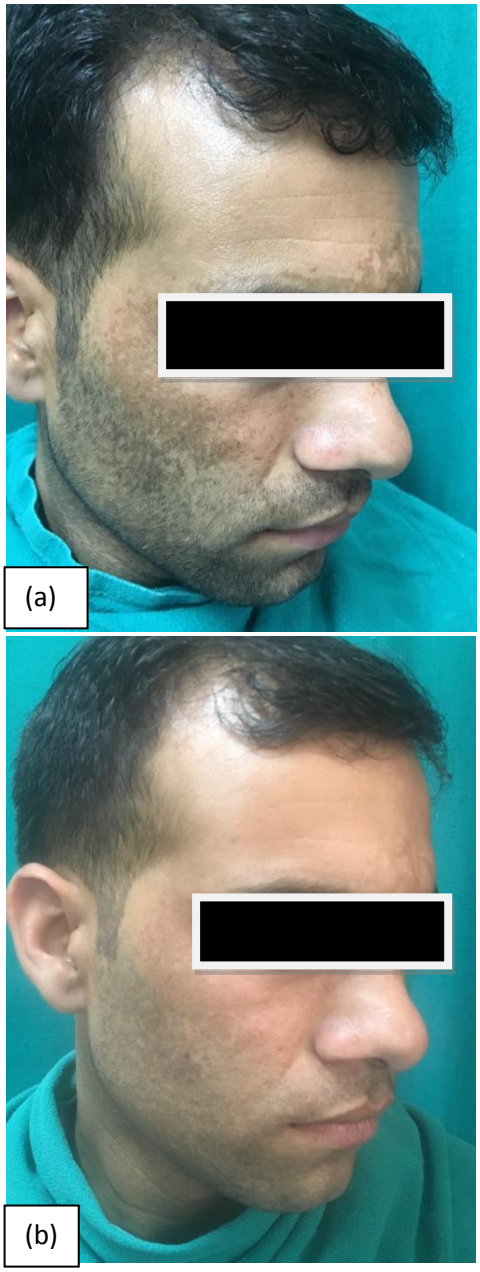

Figure 5: (a) baseline (b) centrofacial pattern showing significant MASI reduction at 8 weeks (after 2 doses)

Of 41 patients who received all the three doses, 15(36.5%) patients showed mild response, 14(34.1%) patients showed moderate response and 2(4.9%) patients had good response, at 4 weeks. At 8 weeks, 19(46.3%) patients had good response, and 15(36.6%) patients showed moderate response. At the end of 12-week study period, good and very good response occurred in 9(22%) and 32(78.0%) patients, respectively (Table-5).

Table-5: Clinical improvement in relation to MASI scores reduction

Clinical response	week 4	week 8	week 12
Very good response (>75% improvement)	-	5(12.2%)	32(78%)
Good response (50-75% improvement)	2(4.9%)	19(46.3%)	9(22%)
Moderate response (25-50% improvement)	14(34.1%)	15(36.6%)	-
Mild response (<25% improvment0	15(36.6%)	2(4.9%)	-
No response	10(24.4%)	-	-

The patients with TXA injections just showed transient oedema and pain at the injection site as the only adverse effects.

Discussion

Melasma is a common, acquired hypermelanosis that affects sun-exposed areas mostly involving the face and has a significant cosmetic and psychological morbidity. It affects all races with a predilection among women with skin phototypes II to VI according to Fitzpatrick's classification but rarely manifests before puberty.[23]The exact prevalence of melasma is unknown but in recent studies ranges from 8.8% to 40% based on ethnic makeup of the population.[24]

In this study, the age group of patients was 18-55 years and comprised 45(90%) women and only 5(10%) men. Melasma is less frequent in men as compared to women, 10% in a study[26], which is similar to our results probably because men consult less often for aesthetic reasons The duration of melasma varied from 5 months to 22 (mean 5.05) years at the time of presentation. Centrofacial pattern in 29(70%) and malar pattern in 12(29%) was observed in our study which is similar to patterns noted by Achar et al[23]and Guinot et al.[27]All these clinico-demographic features corroborate with the reviewed literature.

In 2006, Lee et al,[20] during a prospective study, investigated the effect of localized TA intradermal microinjection (4 mg/mL) on 100 korean women with melasma. About 85 patients completed the study, and a statistically significant decrease was observed in MASI at 8 and 12 weeks. . Steiner et al.[28] in 2009 reported improvement in 66.7%

patients while 22.7% patients had no change with intradermal TXA given every weekly for 16 weeks. Budamakuntla et al.[29] in 2013 noted mean percentage reduction in MASI score in 31.32% at the end of 12 weeks of intradermal TXA microinjections. In 2018, Shetty and Shetty report higher clinical improvement with intradermal microinjection (35.6%) compare to oral tranexamic acid (21.7%) and mMASI score was 11.83±1.72 at the baseline and it reduced to 7.62±1.64 after 12 weeks[30]. However, in our study, 32(78.0%) patients had very good response and 9(22.0%) patients had good response which is similar to observations of other studies. Transient oedema and pain at the injection site were the only adverse effects and did not warrant discontinuation of the treatment. Melasma being a chronic and recurrent disease satisfaction level of these patients remains low for continuation of therapy and regular follow up despite repeated counseling. Although TXA has emerged as a potential treatment for melasma, it has not been approved by Food and Drug Administration of the United States for melasma and treatment remains controversial.[31,32]

Conclusions

Intradermal TXA microinjections were found effective with a significant reduction in MASI score in our study and also appear to be relatively safe except pain at the injection site which may warrant discontinuation of the treatment. However, further large studies are required.

Limitations of the study

- Small number of patients and short duration of the study.
- Lack of long term follow up.
- Use of MASI score, which is a subjective assessment tool.
- No control data could be compared.

Conflict of Interest: None declared.
Financial Disclosures: No funding sources

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