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Tranexamic Acid Mesotherapy for Melasma: An Interventional Study

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ABSTRACT

Background: Tranexamic acid (TXA), an anti-fibrinolytic agent traditionally used to manage blood loss, has shown promising results in the treatment of melasma. Studies on the efficacy of intradermal TXA, with or without adjuvants, in treating melasma remain limited. There is also a lack of consensus on optimal dosing. This study aims to assess the efficacy of intradermal TXA for the treatment of melasma.

Methods: A total of 30 patients aged 20 to 60 years, diagnosed with melasma, were identified at the Department of Dermatology, Benazir Bhutto Hospital, Rawalpindi, Pakistan, from October 2021 to April 2022. 0.05ml tranexamic acid (4mg/ml) was injected intradermally into the melasma lesions at 1cm intervals with a 0.5 mL insulin syringe and a 30-gauge needle. Intradermal TXA injections were repeated weekly for 12 weeks. Baseline and 4-, 8-, and 12-week modified Melasma Areas Severity Index (mMASI) were recorded. Clinical photographs were taken at 4, 8, and 12 weeks.

Results: Ages ranged from 20 to 60 years, with a mean age of 32.17 ± 6.70 years. 90.0% of patients were between 20 and 40 years of age (n=27). The mean baseline mMASI score was 8.58 ± 3.66. Mean mMASI scores at 4, 8, and 12 weeks were noted as 4.88 ± 2.22, 2.83 ± 1.37, and 1.38 ± 0.63, respectively. Over a 12-week treatment course of intradermal TXA, a significant reduction in mMASI score by 7.20± 3.71 was noted (P<0.0001).

Conclusions: Weekly TXA injections (0.05 mL, 4 mg/ml) for 12 weeks resulted in a significant reduction in mMASI score (P<0.0001).

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INTRODUCTION

Melasma is a pigmentary disorder affecting over 5 million people in the United States.[1] The term "melasma" is derived from the Greek root word "melas," which means black, referring to the dark, hyperpigmented macules and patches that are clinically characteristic of this condition.[2] Sun-exposed areas, such as the face, are most commonly involved, particularly the bilateral cheeks, chin, and nose.[2] Melasma is more prevalent in women of childbearing age, especially among those with Fitzpatrick skin types IV-VI and of Hispanic, Asian, African, or Middle Eastern descent. Prevalence ranges from 8.8% among females of Latino descent living in the southern United States, 13.4 to 15.5% in a population of Arab Americans living in southeast Michigan, and up to 40% in some females of Southeast Asian populations.[3-5] In addition to the physical presentation, melasma can impact patients' quality of life, with many reporting frustration, embarrassment, and loss of confidence.[6]

The exact pathogenesis of melasma is complex and multifactorial, and evolving research suggests an interplay of keratinocytes, mast cells, gene regulation abnormalities, neovascularization, and basement membrane disruption.[7] Common triggers include sun exposure, pregnancy, oral contraceptives, hormone replacement therapy, cosmetics, medications, and racial or genetic effects.[8] Ultraviolet exposure results in an increase in melanogenic activity, leading to long-lasting epidermal pigmentation, specifically in darker skin.[9-11] Hormonal influences also play a role in some individuals, given the increased prevalence of melasma during pregnancy, oral contraceptive use, and hormone therapy. Melasma occurs in 14.5% to 56% of pregnant individuals, and 11% to 46% are associated with individuals on oral contraceptives.[12] During pregnancy, the increased production of pituitary hormones leads to the transcription of tyrosinase and dopachrome tautomerase, increasing pigmentation.[13] In addition, estrogen and progesterone have been associated with the disease due to increased expression of estrogen and progesterone receptors on melasma-affected skin.[14] Some cosmetic products have been noted to cause a phototoxic reaction, activating melasma.[15] Family history is another important risk factor, with more than 30% of patients reporting a family history of melasma.[8]

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The treatment of melasma remains challenging, and efficacy varies widely between patients. Current treatments include photoprotection, avoidance of triggers, topical combination depigmenting agents, such as hydroquinone, tretinoin, and fluocinolone, laser therapy, intense pulsed light therapy, microneedling, and chemical peels.[5,10,16-19] Triple combination therapies were found to be more effective than monotherapy treatment of chemical peels, light, and laser therapy; however, 40% of patients developed erythema and peeling.[19]

Oral, topical, and intradermal tranexamic acid (TXA) has been used in the treatment of melasma as it inhibits neovascularization and melanogenesis.[20] Twelve weeks of oral TXA (250 mg BID for 3 months) showed a significant reduction in the modified Melasma Area Severity Index (mMASI) (P<0.05).[12] Oral TXA as an adjuvant to fluocinolone-based triple combination cream also showed a significant reduction in MASI scores at 4 weeks, with maintenance throughout 8 weeks.[21] However, oral TXA poses the risk of various systemic side effects, including thromboembolism, pulmonary embolism, and myocardial infarction.[22] Intradermal tranexamic acid is a relatively new, minimally invasive, and inexpensive treatment modality for melasma. In a prospective, randomized, open-label study of 30 patients receiving intradermal TXA microinjections monthly for 3 months, a 35.72% improvement in MASI score was noted.[23] In a nonrandomized split-face control trial comparing intradermal TXA and normal saline every 2 weeks for 12 weeks, intradermal TXA showed a reduced Hemi-modified MASI score and continued results at a 24-week follow-up.[24] When comparing intralesional TXA to topical hydroquinone, intralesional TXA showed significant improvement in MASI scores, a higher level of patient satisfaction, and fewer side effects.[20,25] An interventional study of 40 patients with melasma demonstrated equal efficacy of oral TXA with transepidermal TXA (with a dermaroller).[26] Batra et al report that although transepidermal TXA was more invasive and painful, this administration avoided the systemic side effects that often deter patients from oral TXA.[26]

Given the high prevalence of melasma in South Asian countries and the varying success of currently available treatments, we present an interventional study in Pakistan that evaluates the efficacy of intradermal TXA injections for patients with melasma in Pakistan.

MATERIALS AND METHODS

From October 2021 to April 2022, adult patients aged 20 to 60 years, diagnosed with melasma, were identified at the Department of Dermatology, Benazir Bhutto Hospital, Rawalpindi, Pakistan. The sampling technique was non-probability consecutive sampling. Exclusion criteria included pregnancy, lactation, oral contraceptive use, active infection, history of herpes simplex lesions on the face, and history of facial warts. 30 patients fulfilling the inclusion criteria were selected. Informed consent was obtained. Patient demographic data, including age, gender, disease duration, and past treatments for melasma, were recorded. All selected patients were clinically evaluated, and the baseline mMASI score was estimated. Modified Melasma Area Severity Index was calculated at baseline as well as at 4-, 8-, and 12-week follow-ups (Figure 1).

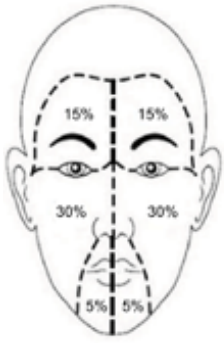
The area (A) of melasma involvement was graded from 0 to 5:

- 0 = No involvement
- 1 = less than 10% involvement
- 2 = 10% to 29% involvement
- 3 = 30% to 49% involvement
- 4 = 50% to 69% involvement
- 5 = 70% to 89% involvement

The darkness of pigmentation (D) and homogeneity (H) were graded from 0 to 4:

- 0 = absent
- 1 = slight
- 2 = mild
- 3 = marked
- 4 = maximum

FIGURE 1. Modified Melasma Area Severity Score (mMASI) grading.



Frontal 15%

Malar 30%

Chin 5%

$0.15(A)(D+H)+0.3(A)(D+H)+0.05(A)(D+H)$

Score: range: 0–24

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

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After applying topical local anesthesia, 0.05 mL tranexamic acid (4 mg/ml) was injected intradermally into the melasma lesion at 1cm intervals with a 0.5 mL insulin syringe and a 30-gauge needle. This procedure was repeated weekly, and clinical photographs were taken at 4, 8, and 12 weeks. The collected data and mMASI scores at baseline, week 4, week 8, and week 12 were analyzed using SPSS 25.0. Means and standard deviations of age, melasma history duration, and mMASI score (pre- and post-treatment) were calculated. A paired sample t-test was performed to compare pre-and post-treatment mMASI scores, with a *P*-value of ≤ 0.05 indicating statistical significance.

RESULTS

Demographics

Demographics of study participants are displayed in Table 1. Eight (26.67%) of the study participants were male, and 22 (73.33%) were female. Ages ranged from 20 to 60 years, with a mean age of 32.17 ± 6.70 years. 90% of study participants (n=27) were aged between 20 and 40 years. The mean duration of melasma history was 6.28 ± 2.50 years. 47% of study participants had tried past treatments for melasma.

mMASI Scores

The efficacy of intradermal TXA was measured in terms of the mean change in mMASI score. The mean change in mMASI score was calculated by the difference in mMASI score achieved at 4 weeks, 8 weeks, and 12 weeks of treatment from the baseline mMASI score. The mean mMASI score after treatment decreased from 8.58 ± 3.66 at baseline to 4.88 ± 2.22, 2.83 ± 1.37, and 1.38 ± 0.63 at 4, 8, and 12 weeks, respectively, as shown in Table 2. Clinical photographs were also taken pre-treatment and at 4, 8, and 12 weeks (Figure 2).

Stratification of mean change in mMASI after 4, 8, and 12 weeks with respect to gender, age, past treatments, and duration of melasma is shown in Table 3. Improvement of mMASI score was statistically significant when stratified for gender, age, past treatments, and duration of melasma ($P<0.0001$). There was, again, a statistically significant improvement in mMASI score ($P<0.0001$). The same stratification was performed with mMASI scores from 12 weeks, which also demonstrated a statistically significant reduction in all mMASI scores.

TABLE 1.

Demographics of Study Participants (n=30)		
Demographics		**Number of Participants (n=30)**
Sex (male/female)	Male	8
	Female	22
Age (years)	20-40	27
	41-60	3
Duration of Melasma (years)	≤5	8
	>5	22
Previous treatments attempted for melasma	Yes	14
	No	16

TABLE 2.

mMASI Score at Baseline and Weeks 4, 8, and 12 After Intradermal TXA Injections (n=30)			
	Mean mMASI score	**Standard Deviation**	***P*-value**
Baseline	8.58	3.66	0.0001
4 weeks	4.88	2.22	
8 weeks	2.83	1.37	
12 weeks	1.38	0.63	

FIGURE 2. Clinical photographs of patients at baseline (A, E), 4 weeks of treatment (B, F), 8 weeks of treatment (C, G), and 12 weeks of treatment (D, H).



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TABLE 3.

Stratification of Mean Change After 4, 8, and 12 Weeks With Respect to Sex, Age, Duration of Melasma, and Previous Treatments for Melasma

Demographics		Mean mMASI score (Baseline)	Mean mMASI score (4 weeks)	*P*-value (4 weeks)	Mean mMASI score (8 weeks)	*P*-value (8 weeks)	Mean mMASI score (12 weeks)	*P*-value (12 weeks)
Sex (male/female)	M	9.58 ± 3.07	6.21 ± 2.89	0.0001	4.16 ± 1.85	0.0001	1.88 ± 0.95	0.0001
	F	8.22 ± 3.85	4.40 ± 1.82	0.0001	4.85 ± 0.73	0.0001	1.19 ± 0.35	0.0001
Age (years)	20-40	8.59 ± 3.73	4.93 ± 2.28	0.0001	2.89 ± 1.43	0.0001	1.41 ± 0.65	0.0001
	41-60	8.47 ± 3.64	4.50 ± 1.87	0.0001	2.35 ± 0.73	0.0001	1.10 ± 0.17	0.0001
Duration of Melasma (years)	≤5	8.08 ± 3.38	5.29 ± 2.52	0.0001	3.11 ± 1.66	0.0001	1.71 ± 0.73	0.0001
	>5	9.02 ± 3.95	4.53 ± 1.94	0.0001	2.59 ± 1.06	0.0001	1.08 ± 0.33	0.0001
Previous treatments attempted for melasma	Yes	8.09 ± 3.97	4.27 ± 2.66	0.0001	2.90 ± 1.91	0.0001	1.36 ± 0.90	0.0001
	No	9.01 ± 3.44	5.42 ± 1.65	0.0001	2.77 ± 0.67	0.0001	1.39 ± 0.26	0.0001

DISCUSSION

Weekly intradermal TXA injections (0.05 mL, 4 mg/mL at 1 cm intervals) over a period of 12 weeks significantly reduce the mMASI score. A statistically significant reduction in mMASI score is expected when gender, age, past treatments, and duration of melasma are stratified. The results of this study align with the limited literature available on the efficacy of intradermal TXA for melasma treatment. Khalili et al present a systemic review of 33 articles evaluating mesotherapy treatments for melasma.[27] The 2021 review found 28 articles about TXA, 4 articles about vitamin C, 2 articles about glutathione, and 2 articles about triamcinolone. Clinical trials of TXA mesotherapy showed similar efficacy to oral TXA; however, with a slower response rate. Clinical trials included in this review show that administration was often performed with an insulin syringe to allow for more control of placement and a 28 to 30 gauge needle for minimal pain. Interval distance was most commonly 1 cm (18 studies). TXA concentrations were most commonly 4 mg/cc (21 studies). Other concentrations included 10 mg/cc (1 study), 20 mg/cc (1 study), 50 mg/cc (1 study), and 100 mg/cc (3 studies). Sessions varied from weekly to biweekly to monthly to every 4 to 6 weeks.

TXA mesotherapy involves little downtime and minimal side effects, consisting primarily of transient bruising, pain, and erythema that is improved with ice pack application.[20,23-27] Khalili et al report that TXA mesotherapy presents as an efficacious adjunctive or alternative therapy for refractory melasma, patients with low compliance with topical treatments, and for those who may have contraindications to oral TXA.[27] The data on intradermal vitamin C, glutathione, and triamcinolone for melasma remain limited. The review emphasizes the importance of further studies to determine ideal concentrations and intervals for TXA mesotherapy. Our study contributes to the current literature by presenting that weekly intradermal TXA injections (0.05 mL, 4 mg/mL at 1 cm intervals) for 3 months in skin types III-VI showed significant reduction in mMASI score and clinical improvement.

CONCLUSION

Weekly TXA injections (0.05 mL, 4 mg/ml) injections over a period of 12 weeks resulted in a significant reduction in mMASI score ($P<0.0001$). This study aims to contribute to the current literature to elucidate the efficacy as well as optimal route and dosing of intradermal TXA injections in the treatment of melasma.

DISCLOSURES

The authors have no conflicts of interest to disclose.

IRB approval status: Reviewed and approved by Pakistan RMU IRB (Reference No.: CPSP/REU/DER-2020-126-1252)

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