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Original Article

Therapeutic evaluation of intralesional tranexamic acid in higher concentration for treatment of facial melasma

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Abstract

Background Melasma is a chronic relapsing hyperpigmentary disorder. As the entire etiopathogenesis of melasma is not well understood, there are chances of development of new therapeutic modalities. Tranexamic acid (TXA) has been used in a variety of formulations; nevertheless, there are few research, data and opinions regarding the optimal dosage of intralesional TXA in melasma.

Methods Total 32 patients were enrolled in our study from January 2023 to June 2023. Injection TXA (0.05 ml) was given intralesionally 1cm apart on entire facial melasma lesion and repeated after every 4 weeks till lesions cleared or a maximum of 6 sessions. Follow up was done at every visit and after 3 months of last session for relapse. Clinical improvement was measured by percentage reduction in mMASI at baseline, at every session and at follow up.

Results More than 50% patients showed good to very good response with significant reduction in mMASI from 8th week onwards as compared to baseline. Most of the patients were satisfied with their recovery following therapy and reported no significant adverse effects.

Conclusion TXA was found to be efficacious in all types of melasma. Better response was seen in epidermal and mixed types in comparison to dermal melasma. We recommend a dosage of 50mg/ml at monthly intervals as optimal dosage for an effective therapy in all types of melasma.

Key words
Melasma; Intralesional; Tranexamic acid; mMASI.

Introduction

Melasma originates from the Greek word ‘melas’ which means black. It is an acquired hyperpigmentary skin disorder which is marked by symmetrical brown patches that are scattered across sun exposed areas of the body such as the cheekbones, forehead, nose, upper lip, chin, neck and forearms.[1] The reported prevalence ranges from 8.8 to 40%. It is more common in women of childbearing age.[2] Causative factors consist of genetic predisposition, exposure to ultraviolet (UV) radiation, pregnancy, hormonal contraceptives, use of cosmetics, and photosensitive medications.[3] Exposure to sunlight plays a crucial role in the development of melasma, as solar radiation has the ability to activate melanocytes by releasing melanogenesis factors.[4] UV radiation can also stimulate the production of alpha-melanocyte–stimulating hormone, corticotropin, and lipid peroxidation.

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Consequently, this leads to an augmentation in the melanin production by melanocytes.[5] The available treatment modalities are sun protection, topical agents, systemic therapies, procedures such as chemical peeling, laser, and microneedling, etc. Ongoing research is being conducted to create an innovative, and safe treatment modality for this condition as it causes significant stress, cosmetic disfigurement, and embarrassment to the patient.

Tranexamic acid (TXA) in melasma was discovered by Nijo Sadako in 1979 and since then it has been used as oral, topical, intravenous and intralesional microinjection formulations at variable dosages.[6] TXA competitively inhibits the activation of plasminogen activator (PA) through reversible interactions with its lysine-binding sites and inhibiting PA from converting plasminogen to plasmin. It also suppresses angiogenesis and the b-FGF induced neovascularization.[7] The structure of TXA is almost similar to the tyrosinase enzyme so it can degrade the activity of tyrosinase enzyme by competitive inhibition.[8] Oral tranexamic acid is safe and convenient but gastrointestinal, menstrual and other systemic side effects are common.[9] Intradermal TXA typically does not exhibit systemic side effects.[10] It provides a minimally invasive pathway that directly administers the medication while also reducing the amount of dosage required.[11] However, it is related with some local adverse effects such as erythema, swelling (disappears within 1 to 2 hours after injection), pain, bruising, hypopigmentation, hyperpigmentation and irritation.

TXA has been used in various formulations for the treatment of melasma but there is paucity of studies on the ideal dosage of intralesional TXA. Most of the studies have been done with lower concentrations of intralesional TXA 4mg/ml, 10mg/ml and 25mg/ml and the results were not very encouraging. Therefore, we intended to determine its therapeutic efficacy at a higher dosage (50mg/ml of TXA) in patients of facial melasma.

Material and Methods

Thirty two clinically diagnosed patients of facial melasma were enrolled in this interventional study, from January 2023 to June 2023 in the Department of Dermatology, Venereology and Leprosy, at a tertiary care centre in North India, after taking approval from the Institutional Ethical Committee.

The following patients were excluded from the study; those with a history of bleeding disorders and thromboembolic events, abnormal coagulation profile, concomitant usage of anticoagulants and photosensitizing medications, patients with psychological disorders, individuals with a known history of allergy to components of sunscreen or topical anaesthetic used in this research, presence of any active skin infection at the site, pregnancy, and lactation.

All the patients were informed about the procedure in detail after providing informed written consent. A detailed dermatological assessment was done. Fitzpatrick skin type was noted in all patients. Morphological type and clinical pattern of melasma was assessed by dermatoscopy. The mMASI score was also calculated at baseline. All enrolled patients were subjected to laboratory tests, complete blood count, bleeding time, clotting time, viral markers and thyroid profile. Patients were advised to wash their face thoroughly with water and mild cleanser. Topical anaesthetic cream (containing 2.5% prilocaine and 2.5% lidocaine) was applied on face for 45 minutes under occlusion before procedure and then wiped off to obtain completely dry skin.

For 50 mg/ml TXA concentration, 0.5ml injection TXA (500mg/5ml) was drawn in an insulin syringe and diluted with 0.5 ml of

normal saline to get a concentration of 50mg/ml of TXA. 0.05 ml was injected intralesionally through a 30 gauze needle insulin syringe on the facial melasma lesion at 1cm intervals. Maximum dose allowed in a single session was 250 mg of TXA. After the procedure, all patients were instructed to apply broad-spectrum sunscreen with SPF 30. This procedure was repeated every 4 weeks till lesions resolved or a maximum of 6 sessions. Clinical response was assessed by serial photography and mMASI at baseline, at very session and at follow up (after 3 months of last treatment session). Patients were observed for any adverse events such as pain, erythema, irritation, hypopigmentation, hyperpigmentation, purpura throughout the study and follow up and were managed accordingly. Treatment efficacy in the form of clinical improvement was measured by percentage reduction in mMASI at every session and at follow up. The data was entered into MS Excel 2013.Collected data was analyzed by using Statistical Package for Social Sciences (SPSS) software version 22.0. Comparisons were carried out by using paired t-test and one way ANOVA test. A p-value <0.05 was considered statistically significant**.**

Results

Thirty two patients were initially enrolled in this study, out of which one patient left the trial due to cardiac surgery, one patient conceived and four patients were lost to follow up. Therefore a total of 26 patients completed the study out of which 21 patients were female and 5 patients were male. The age range in this study was from 22 to 47 years with mean age of 26.19±7.65 years and most of the study participants being in the age group of 41 to 50 years (42.31%). 14 cases (53.84%) had centrofacial pattern, 10 cases (38.16%) had malar pattern and only 2 cases (7.69%) presented with mandibular pattern of distribution. Among the total 26 participants, epidermal, dermal and mixed pattern was seen in 7, 6 and 13 patients respectively on dermatoscopy **(Table 1)**.

The mean mMASI decreased from baseline score of 5.68±3.05 to 5.02±2.87, 3.57±2.13, 3.29±2.11, 3.01±2.04, 2.68±1.99, 3.01±2.49 at week 4^{th}, 8^{th}, 12^{th}, 16^{th}, 20^{th} and at follow up respectively. Statistically significant ($p<0.05$) decline in mean mMASI score started from 8^{th} week onwards. The percentage reduction in mean mMASI was significant ($p<0.05$) at week 4^{th}, 8^{th}, 12^{th}, 16^{th}, 20^{th} and at follow up **(Table 2)**.

Table 1 Demographic data of the participants.

Characteristic	*n (%age)*
Gender	
Male	21 (81%)
Female	5 (19%)
Age in years	
20-30	9 (34.62%)
31-40	6 (23.08%)
41-50	11 (42.31%)
Total	26 (100%)
Mean age	26.19±7.65
Morphological pattern	
Epidermal	7 (26.92%)
Dermal	6 (23.08%)
Mixed	13 (50%)
Total	26 (100%)
Clinical Pattern	
Centrofacial	14 (53.84%)
Malar	10 (38.16%)
Mandibular	2 (7.69%)
Total	26 (100%)

Table 2 Mean modified MASI score at every treatment session.

Duration	*mMASI*		*p-value*
	Mean	*SD*	
Baseline	5.6885	3.05278	
4 weeks	5.0269	2.87159	0.920
8 weeks	3.5769	2.13172	0.023
12 weeks	3.2962	2.11367	0.006
16 weeks	3.0154	2.04425	0.001
20 weeks	2.6885	1.99105	0.001
At follow up	3.0108	2.4921	0.002
% reduction in modified MASI score at every treatment session			
4 weeks	12.5115	12.90616	0.001
8 weeks	38.8192	9.82426	0.001
12 weeks	44.7192	12.46903	0.001
16 weeks	50.2077	12.65982	0.001
20 weeks	56.7500	14.17980	0.001
At follow up	47.5001	22.5214	0.001

Table 3 Mean modified MASI score at every treatment session according to the types of melasma.

mMASI	*Epidermal (n=7)*			*Dermal (n=6)*			*Mixed (n=13)*		
	Mean	*SD*	*p-value*	*Mean*	*SD*	*p-value*	*Mean*	*SD*	*p-value*
Baseline	4.10	1.15		6.88	2.04		5.99	2.52	
At 4 weeks	3.26	1.66	0.421	6.22	2.02	0.792	5.43	2.52	0.578
At 8 weeks	2.34	1.67	0.030	4.58	1.74	0.313	3.78	1.87	0.011
At 12 weeks	2.01	1.54	0.021	4.23	1.78	0.042	3.55	1.85	0.009
At 16 weeks	1.76	1.51	0.001	3.97	1.71	0.032	3.25	1.75	0.001
At 20 weeks	1.46	1.51	0.001	3.65	1.66	0.001	2.91	1.66	0.001
At 3 months	1.21	1.35	0.001	4.50	3.28	0.322	3.29	2.12	0.017

Table 4 Grade of clinical improvement.

Grade of clinical improvement		*Epidermal (n=7)* *no. (%)*	*Dermal (n=6)* *no. (%)*	*Mixed (n=13)* *no. (%)*
Very Good	(>75% reduction in mMASI score)	3 (11.54%)	0	1 (3.85%)
Good	(51-75% reduction in mMASI score)	1 (3.85%)	4 (15.38%)	6 (23.08%)
Moderate	(25-50% reduction in mMASI score)	3 (11.54%)	0	3 (11.54%)
Mild	(<25% reduction in mMASI score)	0	2 (7.69%)	2 (7.69%)
No Response	(no reduction in mMASI score)	0	0	1 (3.85%)

From 8th week onwards, we observed a statistically significant ($p<0.05$) decrease in the mean mMASI score in both the epidermal and mixed melasma cases as compared to the baseline. However, in the dermal pattern, a significant reduction was observed from 12th week onwards ($p<0.05$) but at the follow-up, the reduction was not statistically significant ($p=0.322$) **(Table 3)**.

As per grade of clinical response, very good response was seen in 4 patients, 11 patients showed good response, 6 patients had moderate response, 4 patients showed mild response and only 1 patient did not exhibit any response **(Table 4)**.

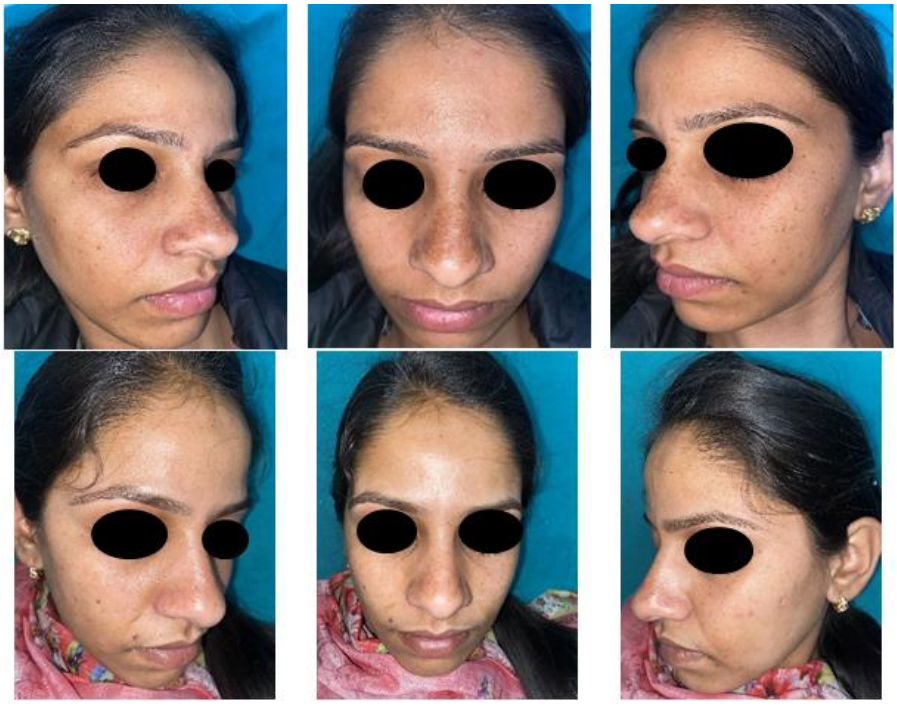

Figure 1 Clinical photographs of 21 year old female with centrofacial epidermal melasma showing significant reduction in mMASI at week 8 in comparison to baseline.

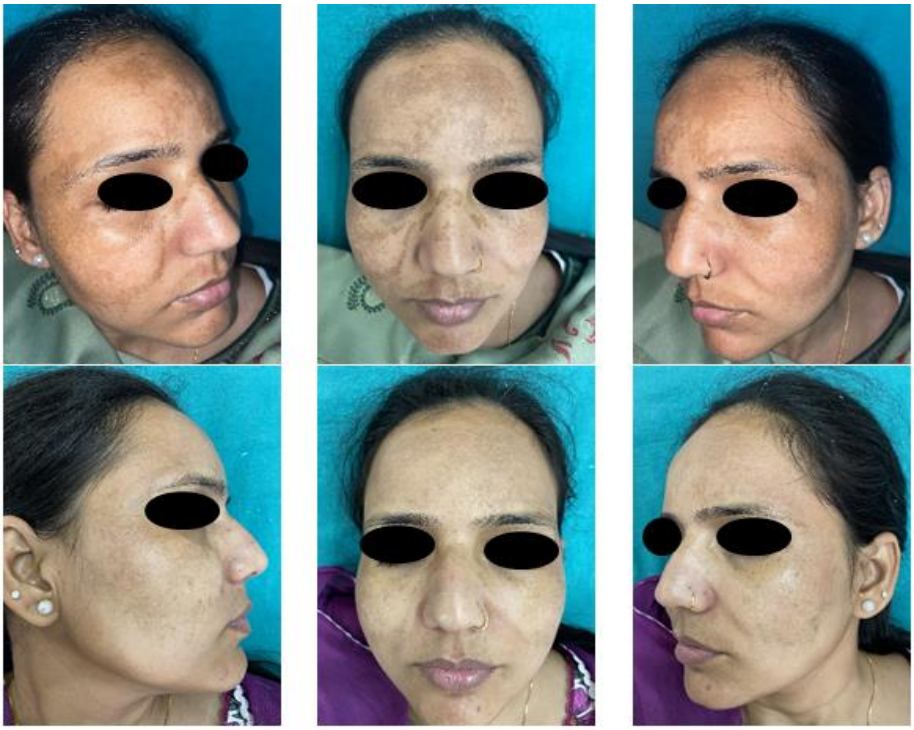

Figure 2 Clinical photographs of 32 year old female with dermal centrofacial melasma showing significant reduction in mMASI after follow up period in comparison to baseline.

Discussion

Melasma is a chronic, relapsing and recalcitrant facial hyperpigmentary disorder. Although various treatment modalities have been tried in the past but no modality has achieved satisfactory results. Therefore, melasma remains a challenging condition that still needs a new effective treatment modality.

In this study 53.84% patients had centrofacial pattern, 38.16% patients had malar pattern and 7.69% patients had mandibular pattern of melasma. A study by Abdalla MA, showed that malar melasma is more common in male patients while centrofacial is common among female patients.[12] Current study included a majority (50%) of participants with mixed pattern, 26.92% patients with epidermal and 23.08% patients with dermal melasma. A study by Khurana *et al;* showed most patients (68.8%) to have mixed pattern.[13]

The mean mMASI score in the present study started decreasing from 4th week onwards and showed statistically significant decline from week 8 ($p<0.05$) until the follow-up period. Similar trend of reduction in mMASI was found in a study done by Wongwicharm P and Sirithanabadeekul P. This study was also done with the same concentration of TXA (50mg/ml), where mMASI score slightly decreased since week 4 and showed statistically significant difference from 8th week onwards including follow up.[14] Studies by Lee *et al;*[15] and Lueangarun S *et al.*[16] noticed a statistically significant decline in MASI score from baseline to week 12th and week 16th respectively. These delayed declines were attributed to the use of a lower concentration (4mg/ml) in both the studies.

The current study demonstrated a statistically significant reduction in mean mMASI from baseline in epidermal and mixed patterns starting from the 8th week and remained significant thereafter. On the other hand, in the dermal pattern, a significant reduction was

observed from the 12th week onwards, but this reduction was not maintained at follow-up. These findings align with a study conducted by Verma Y R *et al;*[17] where a decrease in mean MASI score from baseline in the epidermal melasma group was statistically significant from the 8th week onwards and remained significant at follow-up. However, in the mixed and dermal melasma groups, the mean MASI decreased to a significant level from the 12th week onwards in both cases but did not remain the same at follow-up (24th week) in the case of dermal melasma. This difference could be attributed to the lesser number of treatment sessions (4) and lower concentration of TXA (25mg/ml) used in the study by Verma Y R *et al.* compared to our study, which involved a higher number of treatment sessions (6) and a higher concentration of TXA (50mg/ml). This is also reiterated by two studies conducted by Pazyar N *et al.*[18] and Samanthula H *et al;*[19] which stated that increasing dosage of TXA (100mg/ml) can significantly increase the effectiveness of treatment. Increase in the dose (10mg/ml) and frequency (weekly) of intralesional TXA showed better results without significant adverse effects.

Most of the patients experienced mild burning, pain, and erythema at the site of injection, which eventually disappeared within a few hours. Similar findings were also reported in a study by Pazyar *et al*.[20] Another study concluded that burning & pain were significantly higher in the patients treated with TXA with ascorbic acid than TXA alone.[21] In the present study, none of the patients had any serious local and systemic adverse effects and only 3 patients developed hyperpigmented scarring at the injection site which gradually resolved after few weeks. Similar adverse effect was also noticed in a study by Adelia AL *et al*.[22]

Conclusion

TXA has been used for many years in various formulations for treatment of melasma, but its usage in higher dosages (50mg/ml) as intralesional microinjections has not been studied earlier. TXA in higher concentration was found to be effective for treatment of all types of melasma. Epidermal and mixed types showed extremely convincing results with early and better therapeutic response while relatively lesser response and an early relapse was noted in dermal melasma. Due to the lack of consensus on ideal dosages and frequency, we recommend monthly therapy of TXA at a higher dosage of 50 mg/ml as an effective and time saving treatment modality in all types of facial melasma.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

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Conflict of interest Authors declared no conflict of interest.

Authors' contribution

J: Conception, design the work, acquisition, analysis, interpretation of data, drafting the work.

SS: Conception, design the work, acquisition, analysis, interpretation of data, drafting the work, critical review

GA: Conception, analysis, interpretation of data, drafting the work.

RB: Acquisition, analysis, drafting the work, critical review.

JK: Design the work, interpretation of data and critical review.

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