Original Article

A Randomized Comparative Study of Intralesional Tranexemic Acid and Kligman's Regimen in Indian Patients with Melasma

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Abstract

Context: Melasma is an acquired chronic disorder of hyperpigmentation. Tranexamic acid (TXA) has been shown to be effective in reducing the severity of melasma. **Aims:** The aim of this study is to compare the efficacy of intralesional TXA with topical Kligman's regimen in the treatment of facial melasma and to assess their safety profile. **Settings and Design:** A double arm open-labeled randomized controlled trial was conducted at a tertiary care center in western India. **Materials and Methods:** Sixty-eight cases of facial melasma of either sex and age ≥ 18 years were randomized into two groups. Group A received intradermal injections of TXA 4 mg/mL, whereas group B received topical Kligman's therapy. Patients were evaluated at baseline, 4th, 8th, and 12th week semi-objectively using modified melasma area severity index (mMASI) score, physician's global assessment scale, and patient's global assessment scale. **Statistical Analysis:** Data were analyzed using SPSS v16 software. Mann–Whitney *U*-test, Friedman's analysis of variance test, and Pearson's χ^2 test were used. *P*-value less than 0.05 was considered as statistically significant. **Results:** Fifty-nine patients completed the study. The decrease in mean mMASI score was statistically significant at 4th, 8th, and 12th week for both groups. On intergroup comparison, a statistically significant difference was observed between both the groups at 12th week ($P < 0.01$), with group B showing better response to therapy but no difference at baseline and at 4th and 8th week. Group A showed no significant side effects, whereas group B showed erythema, burning, and hypopigmentation in nine, six, and three patients, respectively. **Conclusion:** Kligman's regimen remains the gold standard for melasma but with multiple serious adverse effects. Intralesional TXA is a safe and promising modality in the treatment of melasma. It can be used in non-responding cases and in those who develop side effects of Kligman's regimen.

Keywords: Intralesional, Kligman's, melasma, tranexamic acid

Introduction

Melasma is a chronic acquired disorder of hyperpigmentation over sun-exposed skin. Females in their reproductive age group are commonly affected, with cheeks, nose, upper lip, and forehead being the predominant areas of involvement.[1] The prevalence of melasma varies between 1.5% and 33.3%, depending on ethnicity, skin phototype, and intensity of sun exposure. Males represent only 10% of the cases.[2,3]

Treatment of melasma is exigent due to progressive nature of the disease and its propensity to recur. Multiple modalities of treatment including topical whitening agents and/or chemical peels along with laser therapy are being practiced with varying degrees of efficacy.[4-6] Hence, there arises the need to evaluate new therapeutic options which are safe, efficacious, affordable, and have better compliance. Studies have shown that the intradermal injections of tranexamic acid (TXA) were effective in decreasing severity of this skin disorder.[7,8]

TXA has been traditionally used for the management of menorrhagia. In dermatology, it has been used orally and as a topical agent or intradermal injection in melasma patients for its whitening effects.[9,10] Localized microinjection was introduced in France by Pistor.[11]

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Its goal is to apply an adequate amount of medication directly to the problem point, to avoid oral medications, and to use lower dosages of drugs. The commercial TXA preparations that are currently available are only tablets and injections. There have been no studies assessing the efficacy and safety of intralesional TXA when compared with the standard treatment of melasma, so this study was conducted to evaluate the comparative efficacy and side effects of this potential new method.[12,13]

Materials and Methods

The primary objective of our study was to compare the efficacy of intralesional TXA injection with topical Kligman's regimen (fluocinolone acetonide 0.01% + hydroquinone 4% + tretinoin 0.05%) in the treatment of facial melasma. The secondary objective was to assess the safety profile of intralesional TXA and topical Kligman's regimen in patients with facial melasma.

The study was conducted in a tertiary care center of western India. It was a double arm randomized controlled trial carried out over a period of 9 months (August 2017 to April 2018) after taking approval from Institutional Ethics Committee. This study is registered in Clinical Trial Registry of India.

Patients of either gender, ≥18 years of age, and attending the dermatology outpatient department (OPD) who were diagnosed with facial melasma were included in the study. The exclusion criteria were women who were pregnant, lactating, or on Hormone replacement therapy/oral contraceptive pills any severe medical illness, bleeding disorders, or concomitant use of anticoagulants; history of pharmacological treatment for melasma within 1 month, hypersensitivity to TXA, abnormal bleeding time, clotting time, or platelet count and presence of other confounding inflammatory facial dermatoses.

The sample size was calculated for 58 patients using Open epi version 3, open source calculator—SSMean calculator—based on the pilot study of five patients in each group as there were no head-to-head studies done before. Considering a drop-out rate of 10%, our sample size was calculated to be 64. Simple random sampling was done using a computer generated randomized list from the website https://www.random.org/sequences.

A detailed history including age, gender, address, education, occupation, duration of melasma, etiological factors (sun exposure, cosmetic use, use of oral contraceptives, phototoxic/photoallergic drugs, anti-epileptics, past pregnancies, menstrual history, thyroid dysfunction, ovarian dysfunction), and family history were noted. An explanation including the risks, benefits, and potential complications was explained to the patients, and written informed consent was obtained from each patient.

Clinical examination included examining pattern of melasma and type of melasma with the help of Wood's lamp. All patients were investigated for bleeding time, clotting time, and platelet count before including them in the study. All patients diagnosed as facial melasma were photographed in three standard views under the same exposure condition. Patients were randomly divided into two groups consisting of 34 patients each using a computer software-generated random number table. Subjects in group A were given intradermal injections of TXA 4 mg/mL of about 0.05 mL at 1 cm spacing every 2 weeks for 10 weeks or till complete clearance, whichever was earlier. Subjects in group B received topical Kligman's therapy (consisting of fluocinolone acetonide 0.01% + hydroquinone 4% + tretinoin 0.05%) daily for 10 weeks or till complete clearance, whichever was earlier. All patients in both groups were prescribed a broad spectrum sunscreen.

Patients in both groups were instructed to return to the OPD every 2 weeks up to 12 weeks. Methods of measurement of outcome of interest were photography, modified melasma area severity index (mMASI), physician's global assessment (PGA) scale, and patient's global assessment (PtGA) scale. At every visit, possible adverse effects were documented.

The data from the case record forms were entered in Microsoft Excel version 2016 and subjected to analysis in IBM SPSS version 16. The data were summarized using frequency, percentages, mean, and standard deviation. The Mann–Whitney *U*-test for non-parametric data, Friedman's analysis of variance (ANOVA) test for before and after comparisons, and Pearson's χ^2 test for categorical data were used. *P*-value less than 0.05 was considered as statistically significant.

Results

Sixty-eight patients participated in this study of which 59 completed the study. Of these, 29 patients belonged to group A and 30 to group B. There was no statistically significant difference between the two groups considering age, gender, duration of melasma, pattern, and type of melasma. Details of the demographic profile are illustrated in Tables 1 and 2.

There were nine drop-outs in the study. In group A, three patients were lost to follow-up due to lack of improvement by 8th week, 2 patients discontinued treatment due to increased pigmentation by the 4th week itself, and one due to side effects of pain and burning. While in group B, one patient discontinued treatment due to erythema at 4th week, one due to unknown reason, and one suffered from post-inflammatory hypopigmentation by 8th week. The details of the reasons for the drop-outs are shown in Table 3.

On intragroup comparison, it was seen that the mean mMASI score decreased from 5.85 (mMASI baseline)

to 4.48 (12th week) in group A, whereas in group B, it decreased from 6.97 (mMASI baseline) to 2.29 (12th week), which was statistically significant in both groups. Details of intragroup comparison are given in Tables 4 and 5.

On intergroup comparison, there was no significant difference in mean mMASI score of baseline, 4th week, and 8th week between group A and group B, respectively. But, statistically significant difference was observed between both the groups at 12th week, as shown in Table 6.

Physician and patient global assessment scores done at 4th, 8th, and 12th week are given in Tables 7 and 8, respectively.

Side effects: Pain and transient burning was experienced by all the cases in group A immediately following the injections. Worsening of melasma was seen in three patients. In group B, major side effects were erythema and burning seen in nine and six patients, respectively. Post-inflammatory hypopigmentation was seen in three patients and worsening of melasma in two patients at 12th week.

Table 1: Demographic profile of study subjects

S. No.	Study variable	Total sample	Group A	Group B	*P*-value
1.	Age (mean ± SD)	35.98 ± 8.62	36.69 ± 10.12	35.30 ± 7.01	0.541
2.	Education				
	0= Uneducated	8	4	4	0.688
	1= Middle school	6	4	2	
	2= High school	20	11	9	
	3= Higher secondary	12	4	8	
	4= Graduate	13	6	7	
3.	Occupation				
	1= Housewife	28	16	12	0.420
	2= Indoor	22	10	12	
	3= Outdoor	9	3	6	
4.	Melasma duration (years) (mean ± SD)	1.8 ± 2.02	1.59 ± 2.01	1.92 ± 2.05	0.467
5.	Number of pregnancies (mean ± SD)	2.82 ± 1.68	3.04 ± 2.07	2.57 ± 1.07	0.356
6.	Number of patients with sun exposure	47	21	26	0.174
7.	Duration of sun exposure (h) (mean ± SD)	1.09 ± 0.83	1.14 ± 0.77	1.06 ± 0.88	0.731
8.	Oral contraceptive pill use	8	4	4	0.959
9.	Cosmetic use	28	12	16	0.358
10.	Sunscreen use	4	1	3	0.317
11.	Family history of melasma	11	4	7	0.347

Discussion

The study participants included 10 (16.9%) males and 49 (83.1%) females with an M: F ratio of 1: 5. Similar clear female predominance was observed in other studies of melasma by Krupashankar *et al.*[14] and Li *et al.*[15] A majority (62.7%) of the patients had malar pattern of melasma similar to that observed in the study by Krupashankar *et al.*[14] In our study, 79.7% had mixed type, 16.9% had epidermal type, and 3.4% had dermal type of melasma. A 2013 study conducted in Brazil showed 43.4% of mixed melasma.[16] Achar and Rathi[17] in their study found 21.47%, 54.49%, and 24.04% of epidermal, dermal, and mixed melasma, respectively. However, recent studies indicate that most cases of the melasma are of mixed type. In our study, Wood's lamp was used to classify melasma. This method is prone to subjective variation in assessment. Facial biopsy was avoided for aesthetic concerns.

In our study, all patients belonged to Fitzpatrick skin type III–V, with the majority belonging to Fitzpatrick group IV (69.5%) followed by group V (23.7%). In a sample of 302 Brazilian patients, 34.4% had skin type III, 38.4% had skin type IV, and 15.6% had skin type V.[16] About 8.6% of the patients in the present study had positive family history of melasma. This is lower in contrast to findings of 31.1% by Krupashankar *et al.*[14] and 38% by Aamir and Naseem.[18] On the contrary, lower frequencies were also identified in Singapore (10%), suggesting that the development of the disease may be under epigenetic hormonal control, as well as the influence of environmental stimuli, such as UV radiation.[19]

Table 2: Patient characteristics in the two groups

Parameters	Group A (*n*) (%)	Group B (*n*) (%)	*P*-value
Fitzpatrick skin type			
III	3 (10.3)	1(3.3)	0.046
IV	23 (79.4)	18 (60)	
V	3 (10.3)	11 (36.7)	
Melasma pattern			
Centrofacial	12 (41.4)	10 (33.3)	0.523
Malar	17 (58.6)	20 (66.7)	
Type of melasma		3 (10)	
Epidermal	7 (24.2)		
Dermal	1 (3.4)	1 (3.3)	0.347
Mixed	21 (72.4)	26 (86.7)	

Table 3: Drop-outs from the study

Reason for drop-outs	Group		Total
	A	B	
No improvement (%)	3 (8.6%)	0 (0%)	3 (1.5%)
Side effects (%)	1 (2.9%)	2 (6.1%)	3 (2.3%)
Worsening of lesions (%)	2 (5.7%)	0 (0%)	2 (0.8%)
Loss to follow-up (%)	0 (0%)	1 (3.0%)	1 (1.5%)
Total (%)	35 (100.0%)	33 (100.0%)	68 (100.0%)

Table 4: Mean mMASI: intragroup analysis

Group	mMASI (week)	Mean	Std. Deviation	Min.	Max.	Mean Rank	p value (Friedman test)
A (*n*=29)	Baseline (0)	5.85	3.54	1.2	15.6	3.17	0.000* (significant)
	4th	5.76	3.48	1.8	15.6	3.17	
	8th	5.01	3.38	1.2	15.6	2.22	
	12th	4.48	3.39	1.2	14.1	1.43	
B (*n*=30)	Baseline (0)	6.97	2.97	1.8	14.2	3.97	0.000* (significant)
	4th	5.00	2.41	1.2	9.9	2.95	
	8th	3.30	1.99	0	8.4	1.90	
	12th	2.29	1.89	0	6	1.18	

*Denotes significant *P*-value

Friedman's ANOVA followed by Bonferroni's correction was applied

Table 5: Detailed intragroup comparison of mMASI

S. No.	Intragroup comparison	Treatment group	*P*-value
1	Baseline vs. 4 weeks	Group A	0.203
		Group B	0.000*
2	Baseline vs. 8 weeks	Group A	0.000*
		Group B	0.000*
3	Baseline vs. 12 weeks	Group A	0.000*
		Group B	0.000*
4	4 weeks vs. 8 weeks	Group A	0.001
		Group B	0.000*
5	4 weeks vs. 12 weeks	Group A	0.000*
		Group B	0.000*
6	8 weeks vs. 12 weeks	Group A	0.001
		Group B	0.000*

*Denotes significant *P*-value

Friedman's ANOVA followed by Bonferroni's correction was applied

Table 6: Mean mMASI score comparison between groups A and B

mMASI (week)	Group	*N*	Mean	Std. deviation	Mean rank	*P*-value
Baseline (0)	A	29	5.85	3.54	26.21	0.094
	B	30	6.97	2.97	33.67	
4th week	A	29	5.76	3.48	31.17	0.605
	B	30	5.00	2.41	28.87	
8th week	A	29	5.01	3.38	34.02	0.076
	B	30	3.30	1.99	26.12	
12th week	A	29	4.48	3.39	36.40	0.005*
	B	30	2.29	1.89	23.82	

*Denotes significant *P*-value

The fall in mean mMASI scores from baseline to 12th week was statistically significant for both groups A and B ($P < 0.05$) on intragroup comparison. This suggests that both treatments are effective for melasma. But, on further intragroup analysis, group B showed statistically significant decrease in mean mMASI scores each between baseline, 4th week, 8th week, and 12th week, whereas group A only showed significant decrease in mean mMASI between baseline and 8th week and baseline and 12th week. This suggests a slow onset of action for intralesional TXA, whereas topical Kligman's regimen shows a faster onset of action which is evident in Figures 1 and 2. This observation is in contrast to early onset of action seen with oral TXA.[8] A possible explanation could be that higher concentrations of intralesional TXA could be possibly required for early onset of action.

While comparing the overall improvement between the two groups, there was no significant difference in mean mMASI scores of baseline, 4th week, and 8th week between groups A and B, respectively. But, statistically significant difference was observed between both the groups at 12th week, with group B showing better improvement.

None of the previous studies has compared the efficacy of intralesional TXA with topical Kligman's therapy. Lee *et al.*,[12] in 2006, injected 0.05 mL of 4 mg/mL TXA intradermally into lesions of melasma, 1 cm apart for 12 weeks with an interval of 1 week, with positive results in a group of 100 Korean women. Eighty-five patients completed

Table 7: Intergroup comparison of PGA

PGA	Clear (90–100%)		Almost clear (75–<90%)		Marked improvement (50–<75%)		Moderate improvement (25 to <50%)		Slight improvement (1 to <25%)		No improvement (0)		Worse (negative)		*P*-value*
Week	A	B	A	B	A	B	A	B	A	B	A	B	A	B	
4th (%)	0	0	0	0	0	0	0	9	4	16	23	5	2	0	0.000
	0	0	0	0	0	0	0	30	13.8	53.3	79.3	16.7	6.9	0	
8th (%)	0	0	0	5	0	3	1	10	7	11	19	1	2		0.000
	0	0	0	16.7	0	10	3.4	33.3	24.1	36.7	65.5	3.3	6.9	0	
12th (%)	0	5	0	2	0	5	3	8	13	8	12	0	1	2	0.000
	0	16.7	0	6.7	0	16.7	10.3	26.7	44.8	26.7	41.4	0	3.4	6.7	

*Pearson's χ^2 test

Table 8: Intergroup comparison of PtGA

PtGA	Completely clear		Nearly clear		Significant hyperpigmentation		*P*-value
Week	A	B	A	B	A	B	
4th	0	0	0	9	29	21	0.001
	0	0%	0	30%	100%	70%	
8th	0	2	1	22	28	6	0.000
	0%	6.7%	3.4%	73.3%	96.6%	20%	
12th	1	8	10	19	18	3	0.000
	3.4%	26.7%	34.5%	63.3%	62.1%	10%	

the trial. A statistically significant decrease in the mMASI from baseline to 8 and 12 weeks was observed, which is in accordance with our study. But in the former study, there was no comparator and the study was not randomized.

In 2009, Steiner *et al.*[20] conducted a study comparing efficacy of TXA for melasma by topical 3% cream and intradermal injections of concentration 4 mg/mL weekly for 12 weeks. On measuring MASI, there was significant improvement (P = 0.0026), with no difference between treatments (P = 0.6512).

A study carried out in Egypt by Elfar and El-Maghraby[21] compared the efficacy of intradermal injection of TXA (group A), topical silymarin cream (group B), and glycolic acid peeling (group C), with 20 patients in each group for the treatment of melasma. Percentage reduction in the mMASI score was evaluated in the three groups: group C showed the highest efficacy, it ranged from 0.0% to 76.0% with a mean of 41.85 ± 22.17%, followed by group B, it ranged from 0.0% to 86.10% with a mean of 39.24 ± 21.27% and the least efficacy was in group A, it ranged from 0.0% to 34.70% with a mean of 20.10 ± 12.15%. The result for intralesional TXA corresponds to our result but the comparators are different. Other similar studies by Budamakuntla *et al.*[22] and Saki *et al.*[23] using TXA microinjections with comparator as TXA with microneedling and topical hydroquinone 2%, respectively, had similar results as in our study with respect to intralesional TXA.

On comparing the other parameters, the PGA grade showed much better response in group B in comparison to group A at all points of time which was statistically significant. PtGA showed statistically significant difference in response in both the groups. Significant hyperpigmentation was present in 62.1% of the group A patients at 12th week, compared with 10% in group B. About 63.3% of the group B patients had near complete clearance at 12th week as opposed to 34.5% in group A.

In group A, none of the systemic side effects of TXA was observed with intralesional therapy. But pain and transient burning were experienced by all the cases which was reduced by using topical anesthesia and ice packs. Worsening of melasma was seen in three patients which can be attributed to post-inflammatory hyperpigmentation due to injection

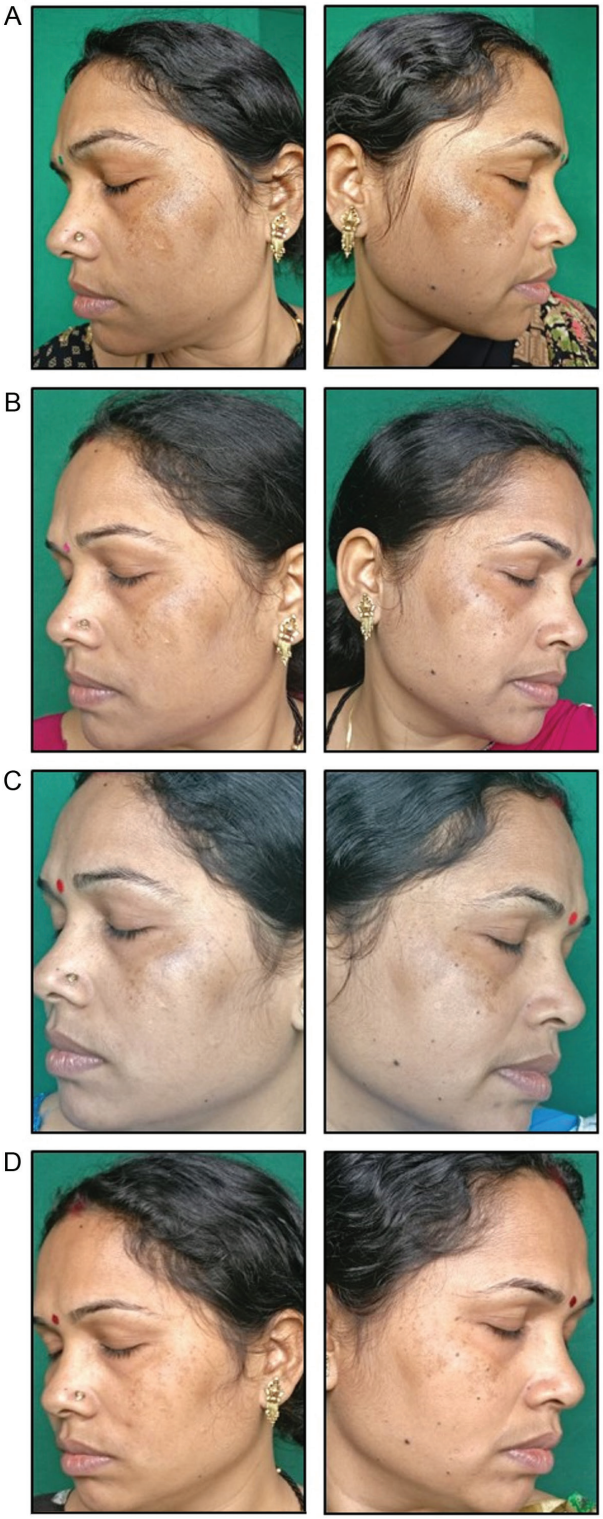

Figure 1: Patient showing improvement in melasma in group A. (A) At week 0, (B) at week 4, (C) at week 8, and (D) at week 12

injury or hematoma formation. In group B, major side effects were erythema and burning seen in nine and six patients, respectively. Post-inflammatory hypopigmentation was seen in three patients and worsening of melasma was seen in two patients at 12th week.

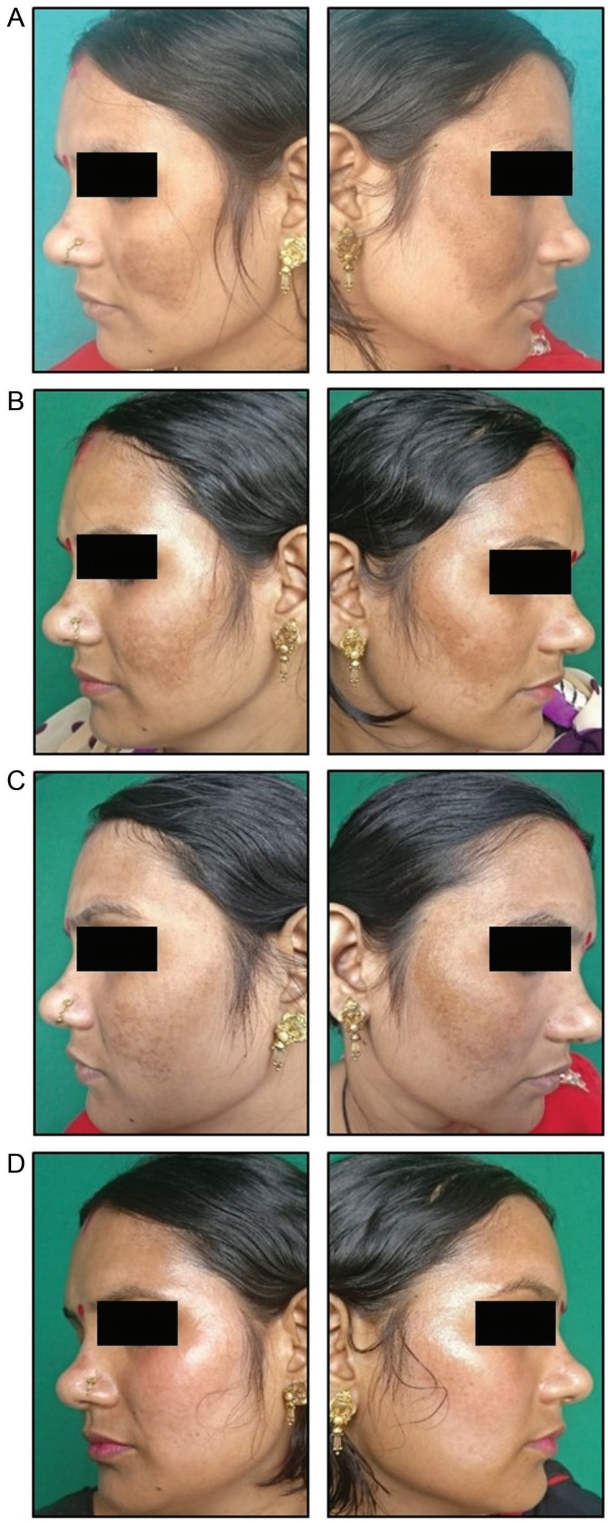

Figure 2: Patient showing improvement in melasma in group B. (A) At week 0, (B) at week 4, (C) at week 8, and (D) at week 12 with post-inflammatory hypopigmentation

Conclusion

Both intralesional TXA and Kligman's regimen are effective modalities for the treatment of melasma. Although topical Kligman's regimen has a better clinical and statistical response at 12th week of treatment ($P = 0.005$) when compared with intralesional TXA, it can act as a double-edged sword due to side effects. These side effects are a limiting factor in using Kligman's regimen, especially when administered for long term.

Intralesional TXA at a concentration of 4 mg/mL given intradermally administered at 2-week interval up to 10 weeks is a safe and promising modality in the treatment of melasma, which can be used in non-responding cases and in those who develop adverse effects of Kligman's regimen. The limitations of our study were lack of long-term follow-up, use of mMASI—a semi-objective tool for analysis, and no dermoscopic evaluation. Lastly, there was no histopathologic correlation used to compare efficacy before and after treatment as multiple facial biopsies were not aesthetically feasible. Further, large multi-center trials and split-face trials with varying and higher concentrations of intralesional TXA are required to arrive at an optimum concentration of intralesional TXA for best results.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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