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Original Research Article

Study of the therapeutic efficacy and safety of intralesional tranexamic acid (25 mg/ml) for the treatment of melasma in male patients: A single centered "before-after" observational study

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ABSTRACT

Background: Melasma is a common and difficult to treat hypermelanosis of poorly understood etiopathogenesis with great tendency to relapse. Tranexamic acid (TA) has been used in various formulations for its treatment, but there is paucity of studies/data and no consensus on the optimum dosage of intradermal TA, especially among the male patients. To study the efficacy and safety of intralesional TA 25 mg/ml for the treatment of melasma in male patients.
Methods: Total 58 males were enrolled for study from July 2019 to June 2020. TA in 25 mg/ml strength injection and about 0.05 ml was injected intradermally at 1 cm apart on the entire melasma lesion, not exceeding 50 mg per visit and repeated every 4 weekly for 12 weeks. The percentage reduction in MASI was the primary outcome measure. It was determined every 4th week till 12 weeks and finally at 24 weeks for recurrence.
Results: Mean MASI decreased from baseline score of 8.42±5.63 to 6.71±4.65, 5.09±3.59 and 3.41±3.06 at the follow up week 4, 8 and 12 respectively with a significant decrease from 8th week onwards. Majority of the patients were satisfied with their improvement after treatment (67.2%) without any significant adverse effects.
Conclusions: However, the TA was found to effective in all the three histopathological types of melasma but the dermal melasma was least responsive as well as earliest to relapse. We recommend monthly therapy at 25 mg/ml as more efficacious, time saving and cost effective to all the three types of melasma.

Keywords: Male melasma, Intralesional tranexamic acid, Mean MASI

INTRODUCTION

Melasma is one of the commonly acquired dermatosis, presenting primarily as a symmetrical, irregular hyper pigmented (tan brown) macules over face, especially the cheeks, nose, forehead, upper lips, chin and rarely on other sun exposed areas like neck, forearms. It has been clinically categorised in to malar 43%, centro-facial 55%, mandibular 2% cases and on woods lamp examination in to epidermal 8-66%, dermal 11-12%, mixed melasma 23-80% patients respectively.[1] The studies on male patients had reported a prevalence ranging from 7.4 to 36.0 % depending on the type of population studied and the region of study.[2] Sarkar et al in their study based on etiological and histological parameters reported that men represent 20.5-25.83% of the total melasma cases.[3]

Etiopathogenesis of melasma is multifactorial, with few commonly known risk factors like, genetic predisposition, UV radiation exposure, hormonal factors such as female sex hormones, thyroid disease, cosmetic contact sensitivity and photosensitising drugs like phenytoin, NSAIDs, tetracyclines, fluoroquinolones act.[1,3] The low testosterone level due to a subtle testicular

resistance, use of diethylstilboestrol therapy for prostate cancer and vegetable oil especially mustard oil on the face, are some of the other recently described etiological factors in males with melasma.[3,4] The disorder is difficult to treat particularly in dark-skinned individuals because there is no universally effective treatment modality and the condition often relapses on discontinuation of topical, laser and systemic therapy. Research is ongoing to develop newer, safer innovative treatment for this disorder that causes profound cosmetic disfigurement, significant psychological stress and embarrassment to the patient.[5] Tranexamic acid (TA) in melasma was a serendipitous discovery by Nijo Sadako in 1979 and since then it has been used in oral, intravenous, topical and intralesional microinjections forms at variable dosages.[6] The various postulated mechanisms of TA in melasma are competitively inhibiting the activation of plasminogen activator (PA) through reversible interactions with its lysine-binding sites and inhibiting PA from converting plasminogen to plasmin.[7] Plasmin can also induce arachidonic acid (AA) production by activated precursors of secretory phospholipid A2. Free AA stimulates melanogenesis via its metabolite, Prostaglandin E2, and leukotrienes.[8] Increased plasmin elevates the α-MSH and bFGF which induces melanocyte activity to synthesize melanin.[9] TA can suppress angiogenesis and the bFGF inducing neovascularization.[7] Human keratinocyte contains both urokinase-type PA and tissue type PA but secretes only single-chain uPA (Sc-uPA). The Sc-uPA which deposits in keratinocyte, results in upregulation of melanocytes, tyrosinase activity, cell parameter and increased dendrite in a dose dependent manner.[10] The amount of Sc-uPA can be increased by plasmin activity. Repeating UV exposure increases the number of mast cells and mast cell tryptase. Tryptase deteriorates type IV collagen. This increases the number of mast cells and tryptase both of which might be a result of basement membrane weakness which is observed in melasma. In the UV exposed skin, the elastin contents are related with the mast cell.[11] The structure of TA is very much similar to the tyrosinase enzyme so TA can completely degrade the activity of tyrosinase enzyme by competitive inhibition.[12]

In melasma, it is mostly used at dosages varying between 250 mg/d and 2.25 g/d, either alone or as adjuvant. The duration of therapy varies across studies from 6 weeks to 6 months and it takes about 1-2 months for the visible effect.[13] Mesotherapy was introduced in France by Pistor in 1958 for applying an adequate amount of medication directly at the problematic area and avoiding oral medications. It offers a minimally invasive route of drug delivery which allows direct delivery of the drug as well as minimizing the dosages.[14] Various studies have been done using intradermal microinjections of TA in the dosages ranging from 4 mg/ml to 50 mg/ml.[15-18] Although melasma has been studied in details in woman, despite several similarities there are many differences in clinical, etiological and therapeutic aspects of melasma in male patients that need to be studied in details. There is paucity of studies/data and no consensus on the optimum dosage of intradermal TA in melasma, especially among the male patients. Therefore, we intended the present research at high dose (25 mg/ml) of TA, in male patients presenting with melasma.

METHODS

Study setting and population

The present study was carried out between July 2019 to June 2020 in the Department of Dermatology, Venereology and Leprosy, Dr. R. P. Government Medical College and Hospital, Kangra at Tanda, Himachal Pradesh, India, as a single centered "Before-After" observational study. All naïve male patients (who has not taken any topical or systemic treatment in past 6 months) with melasma were enrolled after counseling, informed written consent assuring the confidentiality and freedom of choice for participation, presenting consecutively in the outdoor clinic comprised the study population.

Exclusion criteria

Following patients were excluded from the study: patients with history of thromboembolism, bleeding disorders, and abnormal coagulation profile or on anticoagulation treatment, patients with psychological disorders, patients having unrealistic expectations from the treatment, known history of hypersensitivity to TA. who had received any topical or systemic treatment for melasma in last 6 months.

Brief procedure

Clinical examination

Clinical details regarding age, occupation, onset, duration and progress of melasma, aggravating factors, use of medications, and patterns of melasma, both clinical and under Wood's light fluorescence, were recorded. The severity of melasma was accessed by use of MASI score, using the original method introduced by Kimbrough-Green et al.[19] All enrolled patients were subjected to laboratory tests for platelet counts, bleeding time, clotting time and prothrombin index (International normalized ratio/INR) at the beginning (baseline) and at completion of treatment at 12 weeks. The enrolled patients were treated with intralesional TA as per the following protocol.

Treatment protocol

Method and drug preparation

A topical anaesthetic cream (2.5% lidocaine and 2.5% prilocain) was applied on the face for 45 minutes under occlusion. The TA injection was available in the strength of 500 mg/5 ml. Ten units of this injection (i.e., 0.25 ml) were taken in 40 units insulin syringe and mixed with 30

units of normal saline (i.e., 0.75 ml) up to the mark of 40 under strict aseptic conditions to make 25 mg/ml injection. About 2-3 units (0.05 ml) were injected intradermally on the melasma lesion at 1 cm intervals with 30 gauge needle to cover the entire area (Figure 2). Total dose never exceeded 50 mg per visit. The procedure was done at 0, 4, 8, 12th weeks. In between the sessions all participants were advised to avoid excessive sun exposure and to apply a physical sunscreen with a sun protection factor of 30 and avoid the use of any topical preparation/agents on the lesions during the study period. All patients were evaluated for therapeutic outcome and adverse events at weeks 4, 8, 12 and again for recurrence at 24 weeks.

Patient evaluation

The percentage reduction in MASI was the primary outcome measure. It was determined every 4th week till 12 weeks and finally at 24 weeks for recurrence. The pre and post treatment photographic comparison was made to assess and corroborate the therapeutic response by an independent author, other than the author engaged in the injection process. Finally the therapeutic response was graded as: no response (no improvement), mild response (<25% improvement), moderate response (25% to <50% improvement), good response (50% to <75% improvement), very good response (>75% improvement), respectively. Side effects known to be associated with TA as well as other side effects that seem relevant to the treatment were evaluated on every visit. At the end of the study level (week 24th) of patient satisfaction score was also assessed based on five-point Likert scale as per the patient satisfaction level.

Statistical analysis

Data entry was done in MS Excel 2013 and analysis was carried out by Statistical package for social sciences (SPSS) version 22.0. Means and proportions were calculated for continuous and categorical variable respectively. Differences in proportions were tested using chi square test. Difference in means before and after intervention was tested using paired t-test and one way ANOVA. Tests of normality were carried out before hand to ensure normal distribution of data. A $p<0.05$ was considered statistically significant.

RESULTS

Total 125 patients were counseled (all with skin prototype 3, 4, 5) for the study and 83 patients consented for inclusion in the study. But due to unfortunate SARS-COVID-19 pandemic, 25 patients enrolled after December 2019 were lost to follow up on subsequent visits after March 2020 onwards, due to lock down and only 58 patients could complete the study. The drop out noted at each follow-up visit was 12, 9 and 4 patients on 4 weekly interval (Figure 1).

Finally, the base line demographic parameters were statistically analyzed, tabulated and interpreted in (Table 1).

Table 1: Baseline demography of the participants.

Baseline characteristics	Number of patients (n=58) (%)
Total number of patients	58
Age (in years)	
Range	18-43
18-25	20 (34.5)
26-32	26 (44.8)
33-39	9 (15.5)
>39	3 (5.2)
Mean Age±SD	28.22±5.54
Duration of Melasma (in months)	
Range	1-54
Mean±SD	14.45±9.7
Clinical patterns	
Centro-facial	24 (41.4%)
Malar	34 (58.6%)
Mandibular	0 (0%)
Patterns under Wood's lamp	
Epidermal	37 (63.79%)
Dermal	14 (24.11%)
Mixed	7 (12.10%)
MASI score	
Range	2.4-34.2
Mean±SD (n=58)	8.42±5.63
Epidermal (n=37)	8.08±4.86
Dermal (n=14)	9.31±7.97

The age range in the study was from 18 to 43 years with mean age of 28.22±5.54 years, but most of the study participants were in the age group of 18-25 and 26 - 32 years i, e 34.5% and 44.8% respectively. The range of duration of melasma was from 1 to 54 months with a mean duration of 14.56±9.7 months, but most of the study participants (39.7%) had duration of 13 to 24 months. The patients in the study presented only with centro-facial and malar patterns of melasma in 41.4 % and 58.6% cases respectively and none had the mandibular pattern. Among the total 58 participants, 37, 14 and 7 patients had epidermal, dermal and mixed pattern respectively on woods lamp examination (Table 1). MASI range among the participants was from 2.4 to 34.2. The mean MASI decreased from baseline (week-0) score of 8.42±5.63 to 6.71±4.65, 5.09±3.59 and 3.41±3.06 at the follow up week 4, 8 and 12 respectively with a significant decrease from 8th week onwards (p value <0.001). Percentage reduction in mean MASI at week 4, 8 and 12, weeks was 20.3%, 39.55% and 59.50% of the baseline score. However, at week 24th of follow-up we noted further significant decline in the mean MASI (3.18±4.93) as well as in the percentage reduction of

MASI (62.23%) in comparison to the baseline but the reduction was not statistically significant in comparison to week 12th (Table 2).

Table 2: Reduction in mean MASI score and grades of clinical improvement and patient satisfaction scores at 24 weeks.

Follow-up	Reduction in baseline MASI scores	Epidermal (n=37)	Dermal (n=14)	Mixed (n=07)	P value*
Reduction in Mean MASI	Baseline MASI score	8.08±4.86	9.31±7.97	8.39±4.39	---------
	At 4 weeks	6.30±3.70	7.46±7.32	6.77±3.02	0.74
	At 8 weeks	4.78±3.01	5.83±5.19	5.27±2.70	0.65
	At 12 weeks	3.14±2.12	4.07±5.02	3.58±2.40	0.63
	At 24 weeks	2.34±1.61	5.10±9.43	3.26±3.29	0.21
Percentage reduction in mean MASI (%)	At 12 weeks	61.75%	56.28%	57.33%	
	At 24 weeks	71.75%	45.22%	61.14%	
Grade of clinical improvement at 24weeks					
Very good (n=6)	>75% reduction in MASI score	5 (8.62%)	0 (0.0%)	1 (1.72%)	
Good (n=18)	51-75% reduction in MASI score	15 (25.8%)	1 (1.72%)	2 (3.45%)	
Moderate (n=23)	25-50% reduction in MASI score	15 (25.8%)	5 (8.62%)	3 (5.17%)	
Mild (n=9)	<25% reduction in MASI score	2 (3.45%)	6 (10.34%)	1 (1.72%)	
No response (n=2)	No reduction in MASI score	0 (0.0%)	2 (3.45%)	0 (0.0%)	
Satisfaction level	Score on Likert's scale				
Very much satisfied n=6	5	4 (6.89%)	0 (0.0%)	2 (3.45%)	
Somewhat satisfied n=33	4	28 (48.27%)	3 (5.17%)	2 (3.45%)	
Undecided n=12	3	2 (3.45%)	9 (15.51%)	1 (1.72%)	
Not really satisfied n=5	2	3 (5.17%)	0 (0.0%)	2 (3.45%)	
Not at all satisfied n=2	1	0 (0.0%)	2 (3.45%)	0 (0.0%)	

*Significant at <0.05, with 95% confidence interval by One way ANOVA.

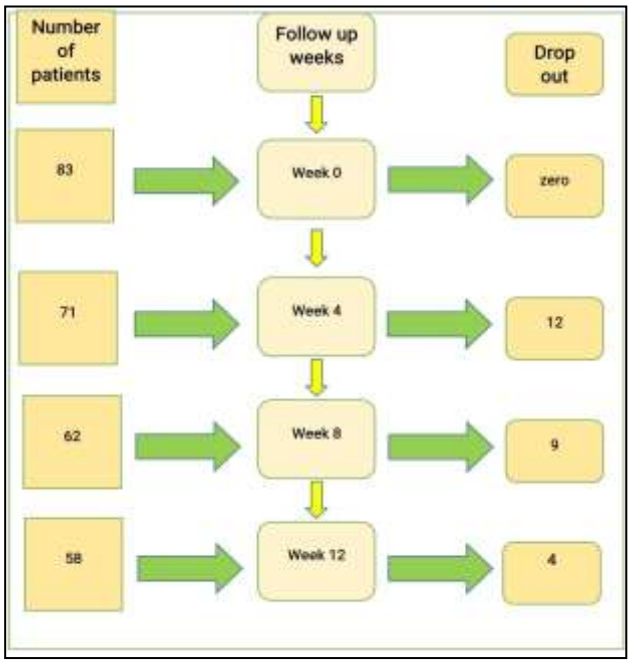

Figure 1: Patient' drop-out at 4 weekly intervals.

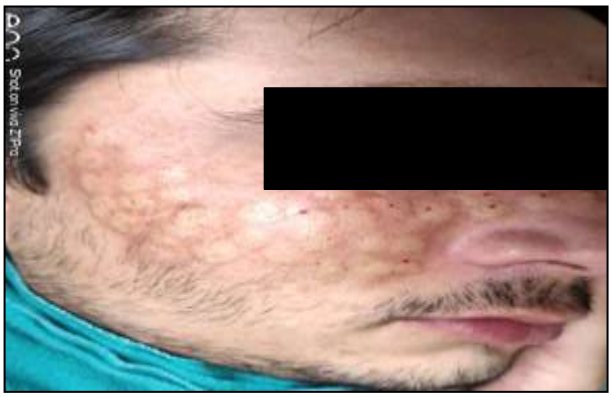

Figure 2: Clinical photograph taken immediately after intralesional TA 25 mg/ml microinjection at 1cm intervals on right side of the face.

Majority of the patients (96.66%) responded to the treatment but with a variable response. 70.68% of the patients showed moderate to good response to the therapy and two patients did not responded at all. Majority of the patients were satisfied with their improvement after treatment (67.2%), however, two patients were not at all satisfied.

Figure 3: Clinical photograph of 29 year old patients with malar melasma showing significant reduction in MASI at week 8 (9.6) and week 12 (1.8) in comparison to baseline/week 0 (14.4), having 87.5% reduction (very good response) in MASI at week 12th.

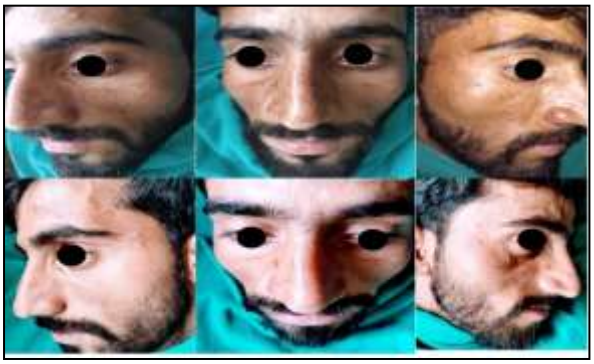

Figure 4: Clinical photograph of 26 year old patient with Centro-facial melasma showing significant reduction in MASI at follow-up week 24th in comparison to baseline/ week-0 i,e MASI 3.6 and 24 respectively, having 85 percent decrease in MASI (very good response).

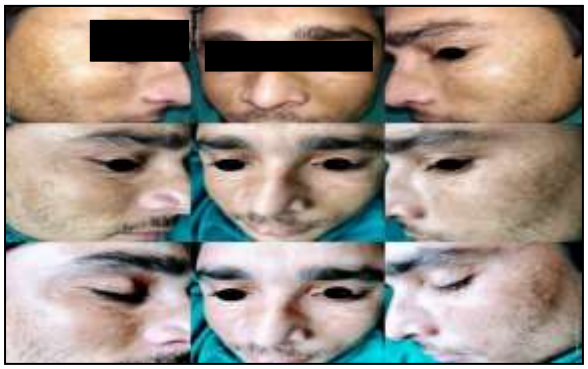

Figure 5: Clinical photographs of the 29 year old patients with centro-facial melasma, showing moderate reduction in MASI at week 8 and 12th (16.2 and 9.3) in comparison to baseline (19.8).

DISCUSSION

Melasma is a well-known disfiguring hypermelanosis of poorly known etiopathogenesis and often recalcitrant to the treatment. The range of age among the participants in our study was from 18 to 43 years with mean age of 28.22±5.54 years with most of the study participants in the age group of 18-32 years (79.3%). The study done by Sarkar et al, had reported the age range from 19 to 53 years with mean age of 30.7 years.[3] The range of duration (in months) of melasma in our study was from 1 to 54 months with a mean duration of 14.56±9.7 months, but most of the study participants (39.7%) had duration of 13 to 24 months, which is less than the duration reported in the literature. Different clinical patterns of melasma have been described and classified clinically on various sites of involvement as centro-facial, malar and mandibular. The patterns were further differentiated on the Wood's light examination as epidermal, which showed an accentuation of pigmentation, whereas dermal melasma did not show any enhancement and some might also have "mixed" pattern.[20] In our study maximum number of the participants had shown malar (n=34; 58.6%) and epidermal melasma (63.79%) on clinical and woods lamp examination respectively. These parameters were comparable to study conducted by Sarkar et al3 malar subtype, clinically as most prevalent in 61% of the patients.[3] In an another study by Khurana et al, among 64 melasma patients, 44 (68.8%) had mixed, 17 (26.6%) had epidermal and 3 (4.7%) had dermal pattern of melasma on woods lamp examination, having a different picture than our study, but the clinical distribution of melasma was centro-facial in 8 (25%) and malar in 24 patients (75%) as in our study.[21] Various treatments are available for treating melasma but without a clear-cut consensus. Hence the present study was undertaken to study the efficacy and safety of intralesional TA at dosage of 25 mg/ml. The mean MASI decreased from baseline (week 0) score of 8.42±5.63 to 6.71±4.65, 5.09±3.59 and 3.41±3.06 at the follow up weeks 4, 8 and 12 respectively, with a significant decrease from 8th week onwards ($p<0.001$). However, at 24th week of follow-up we noted further significant decline in the mean MASI, as well as in the percentage reduction of MASI in comparison to the baseline but the reduction was not statistically significant in comparison to week 12th, a similar trend of MASI fall was reported in a recent study by Lueangarun et al.[22] The percentage reduction in the MASI scores at 12 and 24th weeks were 60.64% and 60.58%, 56.28% and 45.22%, 57.33% and 63.29% respectively, in epidermal, dermal and mixed sub-types of the melasma in the two studies respectively. In our study the decrease in mean MASI from baseline in epidermal melasma group was statistically significant from week 8th onwards and retained the significant p-value at week 12, 24th, where as in mixed and dermal melasma group the mean MASI decreased to significant level from week 12th onwards in both but did not retained the same on week 24th in case of dermal melasma group. However, no statistically significant

difference in the mean MASI decline was noted in the three groups as a whole. Meaning thereby all the three groups responded to the TA intradermal micro-injection therapy well but without any statistically significant difference in each group. However, epidermal melasma responded early to the TA therapy at 8th week, in comparison to the dermal or mixed types, from12th week onwards. Once responded to the treatment the epidermal and mixed subtypes retained the remission, whereas patients of the dermal melasma group failed to retain the same on the last follow up visit at 24th week. This might be due to the effect of sunscreen on the epidermal and mixed subtypes during the follow-up period, but no effect on the recalcitrant nature of dermal melasma, suggesting that the dermal melasma was last to respond and earliest to relapse. However, studies with larger sample size and longer follow up periods are required to validate these findings conclusively. Khurana et al compared TA oral and microinjections in patients with melasma at 250 mg BID versus 4 mg/ml on 64 patients, 32:32 in each group.[21] Pre and post treatment MASI at week 8th were 4.11±2.69 and 2.32±2.56 with a significant p-value (0.047) in intralesional group and the mean falls in the MASI at 0, 8 weeks in epidermal and mixed type was 3.12±4.99 and 1.01±4.81 respectively, not statistically significant (p=0.31) like the findings of our study. Assessment of melasma improvement of 85 patients by Lee et al, has shown in 8 (9.4%) as 51-75% lightening, 65 (76.5%) as 26-50% and 12 patients (14.1%) as poor (0-25% lightening).[23] Similarly, in our study, 6 (10.3%), 18 (31.03%), 23 (39.6%) and 9 (15.5%) patients showed more than 75%, 51-75%, 25-50% and less than 25% improvement respectively. Budamakuntla et al reported that percentage reduction in mean MASI in their study was as 18.39, 28.6, 31.32 and 35.72 percent of the baseline in microinjection group but in our study it was 20.3, 39.5, 59.50 and 62.23 percent of the baseline score at week 4, 8, 12 and 24th respectively.[15] The comparative better results in our study can be attributed to the increased dosage of TA (25 mg/ml versus 4 mg/ml in the two studies).

Lueangarun et al evaluated the efficacy of a 4 mg/ml intradermal TA injection given at 2 weekly intervals in total 7 sessions and the patients were followed up at 4, 8, 12, 16, 48 weeks.[22] There was a significant decrease in mMASI score 42.7% at week 12th in their study, much lower than ours study. Elfar et al observed in their study that intradermal injection of TA leads to significant improvement in melasma, with decline in mean mMASI from 9.37±2.18 to 7.51±2.24 and percentage decrease of 34.70% from baseline, after weekly injections 4mg/ml for 12 weeks.[24] However, the results in our study have shown significantly higher reduction in mean MASI as well as in percentage reduction, concluding that increasing the dose of TA from 4 to 25 mg/ml and frequency of micro-injections to monthly instead of weekly/ fortnightly, can be more beneficial both for the patient as well as treating dermatologist. As it is time saving by decreasing the number of visits/sessions, frequent painful micro-injections and better therapeutic outcome and patient compliance. Sharma et al in their research work stated that better response to treatment was noted with intradermal microinjections of TA 4 mg/ml every 4 weeks as compared to oral TA 250 mg twice daily, with an average percentage reduction of MASI at 12 weeks=79.00±9.64% in intra dermal route.[16] Our study also depicted a significant improvement, with mean percentage reduction in MASI=59.50% after intradermal TA injections at 12th week but less than the mentioned research. Patil et al has proven a decrease in MASI score as statistically significant in intradermal TA group (4 mg/ml) and the score at 0 and 24th weeks were 15.4 and 2.2 respectively, with percentage decrease of 85.71%, against the 62.23% of our study.[25] According to Prapalpitch et al the mean modified MASI score after treatment with TA 50 mg/ml micro-injections, decreased from 2.73±1.07 at baseline to 2.16±1.07, 1.74±0.94, 1.17±0.82 and 1.23±0.79 at week 4th, 8th, 12th, 16th, respectively.[18] The results of the above discussed study agreed with that of the findings noted in our study. The patients' self-assessment of melasma improvement was evaluated at week 16th; 90% as excellent improvement and 10% as good improvement. Self -reported patient satisfaction, in a liker scale, of the present study was also comparable, as majority of the patients were satisfied with their improvement after treatment (67.2%). However, it is to be noted that duration of follow up (24 versus 16) weeks and dosage strengths (25 mg/ml versus 50 mg/ml) were different for these research works but common finding in both the study is definitive better therapeutic outcome by increasing the dosages. Rahim et al found a significant decrease in mMASI in all the three subtypes of melasma and reported most significant decrease in dermal melasma but the percentage decreases in the MASI scores at 12 weeks were almost similar 18.80%, 18.44%, and 17.65% respectively, in epidermal, dermal, mixed sub-types of the melasma, without any statistically significant difference in the response among the three groups, like the results of our study.[26]

In our study, no significant associations were observed between age, mode of onset and type of melasma. Most of the participants (98.3%) in our study had shown no major side effects, except pain, transient erythema/oedema at the injection site, but one patient had post-inflammatory hypopigmentation at the site of injection, after 3rd visit.

Limitations

Involving a comparison group would have improved the validity of the study findings. Observer's bias, as MASI is a subjective scoring system and certainty cannot be 100% even by a single observer, every time calculating the MASI even in the same patient. Short term follow-up cannot predict the remote outcome of the therapy. Small sample size.

CONCLUSION

TA has been used for almost 40 years, in various formulation for treatment of multiple disorders including melasma, but its use in higher dosages i,e 25mg/ml intradermal microinjections has been rarely used, especially in male melasma. TA in the above-mentioned strength is safe and effective modality for treatment of all the three types of melasma, but dermal melasma responded last and relapsed earliest after treatment. There is no consensus among the various researchers on dosages/strength as well as in frequency of microinjections, so we recommend monthly therapy at 25mg/ml as more efficacious, time saving and cost effective to the patients.

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