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Original Article

Efficacy of topical silymarin and intradermal injection of tranexamic acid in the treatment of melasma: A comparative study

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Abstract

Background Melasma is a disorder of pigmentation that results from hypermelanosis. Despite numerous treatment options, response is variable, unsatisfactory, requires prolong course and mostly refractory to available treatments. There is lack of local study and limited international data about silymarin. Intralesional tranexamic acid is now a days an emerging therapeutic tool for melasma.

Objective To compare the efficacy of topical silymarin versus intradermal injection of tranexamic acid in patients of melasma.

Methods Total 72 patients were taken and divided randomly into two equal groups. Group A applied silymarin cream 1.4% two times daily for total 12 weeks on affected areas and group B was given intradermal injections of tranexamic acid 4mg/ml in affected areas at 1cm interval, every week for total 12 weeks. Efficacy was labeled as >50% reduction in modified Melasma Area and Severity Index score from baseline at 12th week.

Results Mean age of the patients was 30.29±7.68 years, 16 (22.22%) were male and 56 (77.78%) were females. Efficacy in Group A was seen in 16 (44.44%) patients and in Group B efficacy was seen in 25(69.4%) patients (p-value=0.03).

Conclusion Intradermal injection of tranexamic acid is more effective as compared to topical Silymarin cream in the treatment of melasma.

Key words
Tranexamic acid; Intradermal injection; Silymarin cream; Melasma; mMASI.

Introduction

Melasma is a pigmentary disorder that results from hypermelanosis and occurs commonly in females of reproductive age.[1] It clinically presents as hyperpigmented macules distributed symmetrically which can be confluent, punctate and reticulated. This disorder mostly prevails in individuals with Fitzpatrick skin type III-V.[2] It affects mostly the ultraviolet light exposed areas specifically upper lips, fore-head, temples and cheeks.[3]

About 5-70% people are affected of which only 10% are males.[4] Melasma negatively effects the patient's life as it can cause psychological

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distress and also disturbs their emotional health and social life.[1,4] This disorder occurs due to over activity of melanin pigment as a result of which the deposition of melanin occurs in the dermal, epidermal layer or both layers of the affected skin.[2]

Treatment of melasma includes sunscreens, topical hydroquinone, topical tretinoin, azelaic acid, kojic acid, local chemical peeling compounds, lasers, dermabrasion, alone or as combinations.[4] Despite numerous options, treatment of choice with lesser side effects still have to be discovered as response is variable, unsatisfactory, requires prolong course and mostly refractory to available treatments. Therefore, to overcome these problems new therapeutic approaches are required.[5]

Silymarin is extracted from milk thistle plant that is Silybum marianum and this plant is the complex mixture of polyphenolic molecules.[6] Its main active constituent silibinin has great antioxidant and anti-inflammatory properties. Dose dependent use of silymarin results in the reduction of melanin production without effecting cell viability.[7,8] According to a study conducted by Elfar and Maghraby,[1] 60 females having melasma were divided in to 3 groups (A, B, C). These patients were treated with injection tranexamic acid (intradermal), silymarin cream and glycolic acid peel respectively. In Group A 0% patients had excellent response, 40% patients had good response. In Group B 5% patients had excellent response, 25% patients had good response. In Group C, 10% patients had excellent response, 30% patients had good response[1]. Another similar study was conducted by Nofal *et al*;[3] in which 42 females with melasma were divided equally in three groups. In this study 28.6% patients treated with silymarin cream 0.7%, 14.3% patients treated with silymarin cream 1.4%, 21.4% patients treated with hydroquinone 4% cream showed good response.[3]

Tranexamic acid is a plasmin inhibitor, reversibly binds to lysine binding sites of plasminogen molecules.[9,10] This results in less free arachidonic acid and lesser production of prostaglandins and decrease in the tyrosinase activity. It has no harmful effect on the healthy non-sun exposed skin.[1,4] A previous study by Lee *et al*. conducted to check localized tranexamic acid efficacy in melasma. In this study 100 females with melasma were selected, in which 9.4% patients showed good response and 76.5% patients showed fair response.[11]

Rationale of this study was that melasma has high prevalence rate and negatively affects patient's quality of life. Despite using multiple treatment modalities, it has a high reoccurrence rate. Intradermal injection of tranexamic acid has more local adverse effects and needs special administration. Treatment with silymarin is cheap and has an advantage of self-administration. There is lack of local study and limited international data about silymarin. So, we wanted to compare efficacy of topical silymarin and intradermal injection of tranexamic acid in order to determine best treatment option for patients of melasma with minimum side effects.

Method

Study was carried out after the approval from the institutional ethical review committee (vide letter No. AMC/PGMI/LGH/Article/Research No/00-207-20, dated 16th November, 2024). It was a randomized control trial of total 72 patients of melasma presenting to the Dermatology unit of Lahore General Hospital, Lahore during six months duration from June to December 2021. Clinically diagnosed patients of symmetrical melasma of either gender, aged between 15 to 45 years, Fitzpatrick skin type III-V, with any type (epidermal, dermal, mixed), severity and duration of melasma were enrolled in this study.

Pregnant and lactating females were excluded. Those patients taking any treatment of melasma during last 3 months, those on oral contraceptive pills in last 1 year, or taking photosensitive drugs (doxycycline) or anticoagulants were also excluded.

Informed written consent was obtained from patients. Patients were randomly allocated in two equal groups of 36 cases each (Group A & B) by lottery method. Information regarding their demographic data (age, gender, duration of illness) was noted in the proforma. Patients were photographed at start of treatment, follow up visits (4^{th}, 8^{th} week) and at the end of treatment.

Group A received silymarin cream 1.4% over affected area twice daily tor 12 weeks and group B was given Tranexamic acid intradermal injections in affected area at 1 cm intervals, weekly for 12 weeks by insulin syringe of 1ml with 30-gauge needle. It contained 0.04ml (4 units of insulin syringe) of Tranexamic Acid and 0.96ml normal saline thus each insulin syringe contained 4mg/ml of tranexamic acid. The modified Melasma Area and Severity Index score was calculated at baseline, at each follow up visits and at the end of treatment. Efficacy was assessed at the end of 3 months treatment and >50% reduction in mMASI score from baseline mMASI score was considered as efficacious. Data was entered in the pre designed Performa and confidentiality of the data was ensured.

The modified MASI Score calculation is done by scoring two components, area and darkness of melasma on face. Face is divided into 4 main areas, right malar (30%), left malar (30%), forehead (30%) and chin (10%).

For Area (A) of involvement, a numerical value is assigned according to affected area assessed in percentages. 0 means no area involved, 1= <10% area affected, 2= 10-29% area affected, 3= 30-49% area affected, 4= 50-69% area affected, 5= 70-89% area affected, 6= 90% or > 90% area affected.

For Darkness of melasma (D), skin is compared to normal skin and graded on scale:

0= normal skin color

1= slightly visible pigmentation

2= Mild hyperpigmentation

3= Moderate hyperpigmentation

4= Severe hyperpigmentation.

Total range of mMASI score is 0 to 24 and it is calculated by adding score of four areas of face.

mMASI total score = $0.3 \times A$ (right malar) $\times$ D (right malar) + $0.3 \times A$ (left malar) $\times$ D (left malar) + $0.3 \times A$ (forehead) $\times$ D (forehead) + $0.1 \times A$ (chin) $\times$ D (chin)

Data was analyzed by using SPSS version 24.0. Age, duration of disease and mMASI score at baseline & post treatment were presented as mean and standard deviation. Gender, site of lesion and efficacy were presented as frequency and percentages. Data stratification for age, gender, site of lesion, severity and duration of disease was done to address effect modifiers. Comparison of efficacy in both groups and post stratification was done by Chi Square test keeping P-value ≤ 0.05 as statistically significant.

Results

In this study total 72 patients were enrolled. The mean age of the patients was 30.29±7.68 years. Mean age in Group A was 28.64±6.91 years and in Group B was 31.94±8.15 years. In our study 16 (22.22%) were males and 56(77.78%) were females. Female to male ratio of the patients was 3.5:1.

The study results showed that the mean duration of lesion of the patients was 5.042±2.75 months

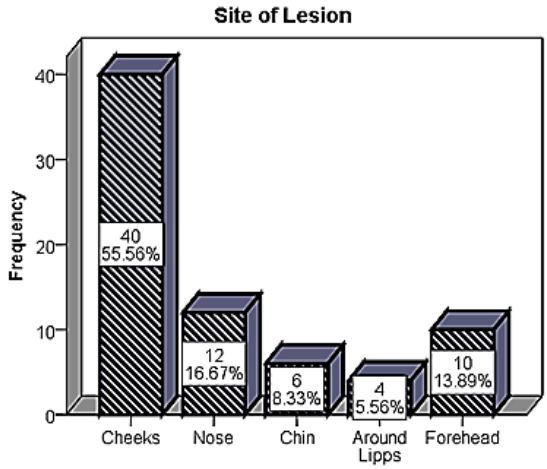

Figure 1 Frequency distribution of lesions according to site.

Table 1 Comparison of mMASI between groups and change in mMASI.

mMASI	*Group A*	*Group B*	*p- value*
Baseline	10.91±4.95	13.36±4.93	0.039
End of treatment	6.33±3.74	5.67±2.89	0.405
Change	4.3±1.95	7.58±3.11	<000.1

with minimum and maximum duration of 1 and 12 months respectively. The mean duration of lesion of the patients in group A was 5.31±2.72 months and in group B was 4.78±2.79 months.

Out of 72 patients, 18 (50%) patients in Group A and 22 (61.6%) patients in Group B had lesions on cheeks. Frequency of distribution of lesions according to site is shown in (**Figure 1).**

In Group A, out of 36 patients, there were 8 (22.22%) patients with mild disease, 18 (50%) patients with moderate disease and 10 (27.78%) with severe disease while in Group B out of 36 patients, 4 (11.12%) patients were having mild disease, 18 (50%) patients with moderate disease and 14 (38.89%) patients had severe disease.

At baseline: the mean mMASI score of patients in group A was 10.91±4.95 and in Group B was 13.36±4.93 (p-value=0.039). At end of the treatment: the mean mMASI score of patients in Group A was 6.33±3.74 and in Group B was 5.67±2.89 (p-value=0.40) **(Table 1)**. In Group A, mean change in mMASI score was 4.3±1.95 while in Group B it was 7.58±3.11. The difference was statistically significant i.e. p-value <0.05.

Results of our study showed that 16 (44.44%) patients out of 36 in Group A achieved efficacy. On the other hand 25 (69.4%) patients out of 36 in Group B showed efficacy to treatment. This difference was statistically significant i.e. P-value 0.03. Out of 72 patients 20 (55.56%) in Group A and 11 (30.6%) in Group B did not show efficacious results **(Table 2)**.

Stratification of efficacy with respect to age, gender, duration and site of lesions did not show any statistically significant difference (p value was > 0.05) **(Table 3)**.

Discussion

Melasma, is a highly prevalent hyper-pigmentary disorder commonly found in Asian and Latin American females. About 5-70% of people are affected worldwide. It has significant effect on patient's quality of life, and emotional health.[12] Principles of therapy include UV protection, suppression of melanocyte activity, melanin synthesis, disruption and removal of melanin pigments.[1] For the treatment of melasma various treatments options are available, in which sunscreens are mostly used in combination with other components like steroids, tretinoin, local chemical peeling

Table 2 Comparison of efficacies of both groups.

Groups	*Efficacy*		*Total*
	Yes n(%)	*No n(%)*	
Group-A (Silymarin)	16 (44.4)	20 (55.6)	36
Group-B (Tranexamic acid)	25 (69.4)	11 (30.6)	36
	P value 0.03		

Table 3 Stratification of data.

		Efficacy	*Group A*	*Group B*	*p-value*
Age (years)	≤30	Yes	11 (44%)	11 (64.7%)	0.187
		No	14 (56%)	6 (35.3%)	
	>30	Yes	5 (45.5%)	14 (73.7%)	0.122
		No	6 (54.5%)	5 (26.3%)	
Gender	Male	Yes	2 (33.34%)	7 (70%)	0.152
		No	4 (66.6%)	3 (30%)	
	Female	Yes	14 (46.7%)	18 (69.2%)	0.088
		No	16 (53.3%)	8(30.8%)	
Duration of lesions (months)	≤6	Yes	12 (48%)	19 (73.1%)	0.066
		No	13 (52%)	7 (27%)	
	>6	Yes	4 (36.36%)	6 (60%)	0.278
		No	7 (63.64 %)	4 (40%)	
Site of lesions	Cheeks	Yes	8 (47%)	15 (59%)	0.183
		No	9 (53%)	7 (41%)	
	Others	Yes	8 (42%)	10 (54.5%)	0.094
		No	11 (58%)	4 (45.5%)	

compounds, laser monotherapy or dermabrasion[4]. Despite multiple treatments melasma is refractory to many therapeutic modalities and it has high relapse rate.[12,13]

Silymarin is extracted from milk thistle plant that is Silybum marianum[6]. It is a potent antioxidant that reduces and suppress harmful effects of ultraviolet radiations (UVR) of sunlight.[7,8] Recently, Tranexamic acid (TA) was introduced as a therapy for melasma.[14] The rationale of using intralesional injection of TA in melasma is that it has no systemic side effects and it is cost effective.[15]

Total no. of patients in this study was 72. Mean age of patients was 30.29 with age range from 16 to 45 years. Elfer and El magharby *et al.*[1] conducted a study in which mean age of patients was 40.07 with age range from 28 to 52 years which is higher than in our study**.** Out of 72 patients in this study, 43.1% (n=31) were in age group of < 30 years and 56.9% (n=41) were in age group >30 years .This was similar to a study conducted by Elfer and El Magharby *et al***.[1]** in which majority of patients were above 30 years of age i.e. 66% (n=40).[1]

Our study showed that out of 72 patients, 22.2% (n=16) were males and 77.8% (n=56) were females. Sharma *et al.*[16] conducted a study in which out of 100 patients, males were 8% (n=8) and females were 92% (n=92) which is comparable to our study in which females were more than males.[16]

In our study, out of 72 patients, 40 (55.6%) patients had lesions on cheeks, 12 (16.7 %) on nose, 10 (13.9%) on forehead, 6 (8.3%) on chin and 4 (5.6%) around lips. A study conducted by Elfer and El Magharby *et al*. showed that out of 42 patients, 32 (76.2%) patients had centrofacial involvement and 10 (23.80%) patients had involvement of malar area[1]. This was comparable to our study in which most of patients had centrofacial involvement. In our study, duration of melasma was from 1 month to 1 year, whereas in a study conducted by Ahmad nofal *et al*.[3] it was between 3 months to 20 years.[17]

In the current study we compared efficacy of topical silymarin cream (Group A) and intradermal injection of tranexamic acid (Group B). Efficacy was seen in 16 (44.44%) patients in Group A and in Group B 25 (69.4%) patients showed efficacy (p-value=0.03). Elfar and El-Maghraby *et al*.[1] conducted a study in 2015 and compared tranexamic acid intradermal injection (Group A), silymarin cream (Group B) and glycolic acid peel (Group C). Group B showed highest efficacy with mean of 41.85%, followed by (Group A) mean 39.24% and the least efficacy was seen in Group C with mean of 20.10%. These results were contrary to our study in which Group B (intradermal tranexamic acid) showed higher efficacy.[1]

Sharma *et al.* and Shetty *et al.* conducted studies and compared oral tranexamic acid and intradermal injection of tranexamic acid. Results of studies showed that intradermal tranexamic acid injections had better efficacy and these results were also comparable to our study.[16-18]

In our study mMASI score in Group A at the end of treatment was decreased from 10.91±4.95 (Baseline) to 6.33±3.74 (at 3rd month). The mMASI score in Group B at the end of treatment was decreased from 13.36±4.93 (Baseline) to 5.67±2.89 (at 3rd month). In a study conducted by Elfar and El-Maghraby *et al*.[1] mMASI score in Group A (intradermal injection of Tranexamic acid) was decreased from 9.37±2.18 (Baseline) to 7.51±2.24 and in Group B (topical silymarin cream) mMASI score was decreased from 10.55±2.60 (Baseline) to 6.46±2.75. These results were not comparable to our study in which Group B has a more reduction mMASI score at end of treatment.

In this study, no side effects were seen in Group A while in Group B all patients had mild erythema and edema that subsided within 24hrs.

In our study, melasma showed response to both treatment options but statistically significant better efficacy was seen in intradermal tranexamic acid group as compared to silymarin group. Treatment with intradermal tranexamic acid injection is a new and emerging treatment option for melasma with minimal side effects.

This study was conducted at a single centre and sample size was small. Therefore, it is recommended that in order to reduce bias, future research be multicentric and conducted with a bigger sample size. A short follow-up period was another research constraint, thus long-term follow up in melasma patients should be done in future studies.

Conclusion

Results of our study concluded that intradermal injection of tranexamic acid has statistically significant more efficacy than topical silymarin in the treatment of melasma.

Intradermal injection of tranexamic acid appears to be a promising therapeutic tool that can be done in outpatient settings. It provides relatively rapid results without significant side effects.

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

AN,FB: Substantial contributions to concept, study design, acquisition of data, analysis and interpretation of data, manuscript writing and critical review, has given final approval of the version to be published.

KT: Substantial contributions to concept, study design, Critical review, manuscript writing, has given final approval of the version to be published.

GSMT,AS: Substantial contributions to acquisition of data, manuscript writing, has given final approval of the version to be published.

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