

Efficacy of Intra-dermal Injection of Tranexamic Acid, Topical Silymarin and Glycolic Acid Peeling in Treatment of Melasma: A Comparative Study

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Abstract

Background: Melasma is one of the most common causes of facial hyperpigmentation which causes cosmetic disfigurement and leads to psychological problems. Although various treatments are available for melasma, it remains a difficult condition to treat.

Aim of the Work: to evaluate and compare the efficacy of intra-dermal injection of tranexamic acid, topical silymarin cream and glycolic acid peeling in treatment of melasma.

Patients and Methods: Sixty female patients with melasma were divided into 3 groups: group A; 20 patients were treated with intra-dermal injection of tranexamic acid. Group B; 20 patients were treated with topical silymarin cream and group C; 20 patients were treated with glycolic acid peeling 50%. Dermoscopic examination and clinical assessment (according to the modified Melasma Area and Severity Index) were performed for all patients.

Results: There was a statistically significant difference between the studied groups as regard the response to different therapeutic modalities with the best results in group C followed by group B then the least response was in group A. There was statistically significant difference between A and B, A and C; so group B and C showed better response than group A, while there was no statistically significant difference between groups B and C.

Conclusion: Silymarin cream was a novel, effective and safe treatment modality for melasma especially in epidermal and mixed types in Fitzpatrick skin phototype III, IV and V as it showed a significant improvement of melasma lesion. It was as effective as 50% glycolic acid peeling in the treatment of melasma without post inflammatory hyperpigmentation that occurred by glycolic acid peeling.

Keywords: Melasma; Tranexamic acid; Silymarin cream; Glycolic acid; Peeling

Introduction

Melasma is a common disorder of hyperpigmentation that occurs most commonly in females during reproductive age. It is most prevalent in darker-complexioned individuals [1]. Melasma, though benign, can be extremely psychologically distressing and has been shown to have a significant impact on quality of life, social and emotional wellbeing [2].

Tranexamic acid (TA); a plasmin inhibitor, inhibits ultraviolet induced plasmin activity in keratinocytes by preventing the binding of plasminogen to the keratinocytes, which ultimately results in less free arachidonic acids (AA) and a diminished ability to produce prostaglandins, and this decreases melanocyte tyrosinase activity [3]. Silymarin has potent antioxidant properties, reduces and suppress harmful effects of solar ultraviolet radiation (UVR) [4]. Glycolic acid (GA) peels effect is derived from its chemexfoliating properties which depend on facilitating the removal of melanized keratinocytes, leading to melanin pigment loss and acceleration of skin turnover [5].

So, the aim of this study was to evaluate and compare the efficacy of intra-dermal injection of tranexamic acid, topical silymarin cream and glycolic acid peeling in treatment of melasma.

Patients and Methods

Sixty female patients with melasma were included in this study. All patients were recruited from the Outpatient Clinic of Dermatology and Venereology Department, Tanta University Hospital from the period of January 2013 to February, 2014. The study was approved by the Research Ethics Committee. All participants signed on informed consent before participation in the study.

Patients with history of hormonal therapy, contraceptive pills (during the last 12 months), bleeding disorders or concomitant use of anticoagulants, topical treatment e.g. hydroquinone (one month before the study), active herpes simplex, facial warts or active dermatoses, history of hypersensitivity to some of the components of the formula of the study, pregnant or lactating females and patients with unrealistic expectations were excluded.

All the patients were subjected to complete history taking and examination: with regard to onset of melasma, duration, family history

and aggravating factors. Also, Fitzpatrick skin type, pattern of melasma (centrofacial, mandibular, malar) [6] was noted.

Wood's lamp examination [7] was done for all patients to determine the type of melasma (dermal, epidermal, mixed).

Digital and dermoscopic photographs were taken for all patients at baseline and after end of the follow up period. The patients were followed up monthly for 3 months after the last session to detect any recurrence or complications.

Assessment of the clinical efficacy of the therapeutic procedures:

Two dermatologists were asked to record the percentage of improvement for each patient after end of the treatment. Scoring of the patients according to modified Melasma Area and Severity Index (mMASI) score [8] before and after treatment was done.

Efficacy of the treatment = $(\text{mMASI score before} - \text{mMASI score after}) / \text{mMASI score before} \times 100$. Clinical efficacy was categorized into: Excellent response; if more than 75% fall in mMASI score. Very good response; if 50-75% falls in mMASI score. Good response; if 25-50% falls in mMASI score. Poor response; if less than 25% fall in mMASI score. No response: when there was no change in mMASI score at the end of the therapy. Patients were classified into:

Group (A): included 20 patients were treated with intradermal injection of 0.05 ml of tranexamic acid solution in normal saline (4mg/ml) into the melasma lesion at 1 cm interval by using sterile insulin syringe, weekly for 12 weeks.

Group (B): included 20 patients were treated with topical silymarin cream (14mg/ml) was applied with amount about one finger tip of cream to cover the affected area of melasma, twice daily for 12 weeks.

Group (C): included 20 patients were treated with 50% glycolic acid peeling within a period of 20-30 seconds started at the forehead, continued to the cheeks, the chin and then the nose. The peel was terminated by the dilutional effect of washing with cold water when erythema occurred. Every 2 weeks for 12 weeks.

Preparation of the formulations was done at the laboratory of the Technological Pharmacology Department, Colleague of Pharmacology, Tanta University.

1. **Tranexamic acid sterile solution:** The tranexamic acid (Kapron) ampoules were diluted with normal saline under aseptic

conditions to produce a sterile solution containing the drug at a concentration of 4 mg/ml.

2. **Silymarin cream:** Semisolid emulsion based system was employed in the current study. Silymarin cream was prepared according to the following formulation: Silymarin powder 1.4g, cetyl alcohol 5 g, stearic acid 3.5 g, Vaseline 14.5 g, tween 80 (7 g), propylene glycol 8 g, distilled water 41 ml. The prepared formulations were packed in air tight containers. Freshly prepared formulation was delivered to patients every week.
3. **Glycolic acid solution:** A stock solution of glycolic acid (70% w/v) was diluted with distilled water to prepare a solution containing (50% w/v).

Statistical presentation and analysis: Statistical presentation and analysis of the present study was conducted, continuous variables are presented as means \pm SD and discrete variables are shown as percentages. Both w2 and Fischer w2 testing were used for intergroup comparisons, and P less than 0.05 was considered significant. Software (SPSS, version 16.0 statistical package for Microsoft Windows; SPSS Inc., Chicago, Illinois, USA) was used throughout.

Results

In this study; there was no significant difference among the studied groups regarding the clinical data as regards age, duration, predisposing factors, Fitzpatrick skin phototype, pattern of melasma and Wood's light examination of the patients (Tables 1 and 2).

The most detected pattern of melasma was the centrofacial pattern and skin phototype IV was the most common detected Fitzpatrick skin phototype. Regarding the Wood's light examination in the different studied groups, there were 30 patients (50%) with epidermal type, 13 patients (21.7%) with dermal type and 17 patients (28.3%) with mixed type.

Dermoscopy of melasma lesions demonstrated a fine brown reticular pattern superimposed on a background of faint light brown areas (Figure 1A) in all studied patients. Also, telangiectasias (Figure 1B) were observed in 40 patients (60%).

Regarding modified MASI score before and after treatment in the different studied groups, there was a highly statistically significant difference of percentage of change in mMASI score after treatment among the three studied groups (Table 3).

		Group A (n=20)	Group B (n=20)	Group C (n=20)	Test of Sig	p
Age of patients	Range	28.0–45.0	29.0–55.0	28.0–50.0	F=3.123	0.052
	Mean \pm SD	37.0 \pm 4.80	41.05 \pm 7.67	36.45 \pm 6.28		
Duration of disease (years)	Range	2.0-10.0	1.0-20.0	2.0-16.0	KW χ 2=4.792	0.091
	Mean \pm SD	6.15 \pm 2.35	8.40 \pm 5.21	5.65 \pm 3.95		

Table 1: Comparison among the studied groups according to age of patients and duration of melisma.

Regarding the clinical efficacy of treatment in the different studied groups, group C showed the highest efficacy, it ranged from (0.0-76.0%) with a mean of (41.85 \pm 22.17%) followed by group B, it ranged from (0.0-86.10%) with a mean of (39.24 \pm 21.27%) and the least efficacy was group A, it ranged from (0.0-34.70%) with a mean of (20.10 \pm 12.15%). There was significant difference between the studied

groups as regard the efficacy (p value=0.003*) with the best results in group C followed by group B then the least efficacy was group A. Comparison among the studied groups with each other regarding their efficacy revealed that, there was a statistically significant difference between group A and both (B and C) groups so, group A was less effective than group B and C. While there was no statistically

significant difference between groups B and C as regard the efficacy (p value=0.675) (Table 4).

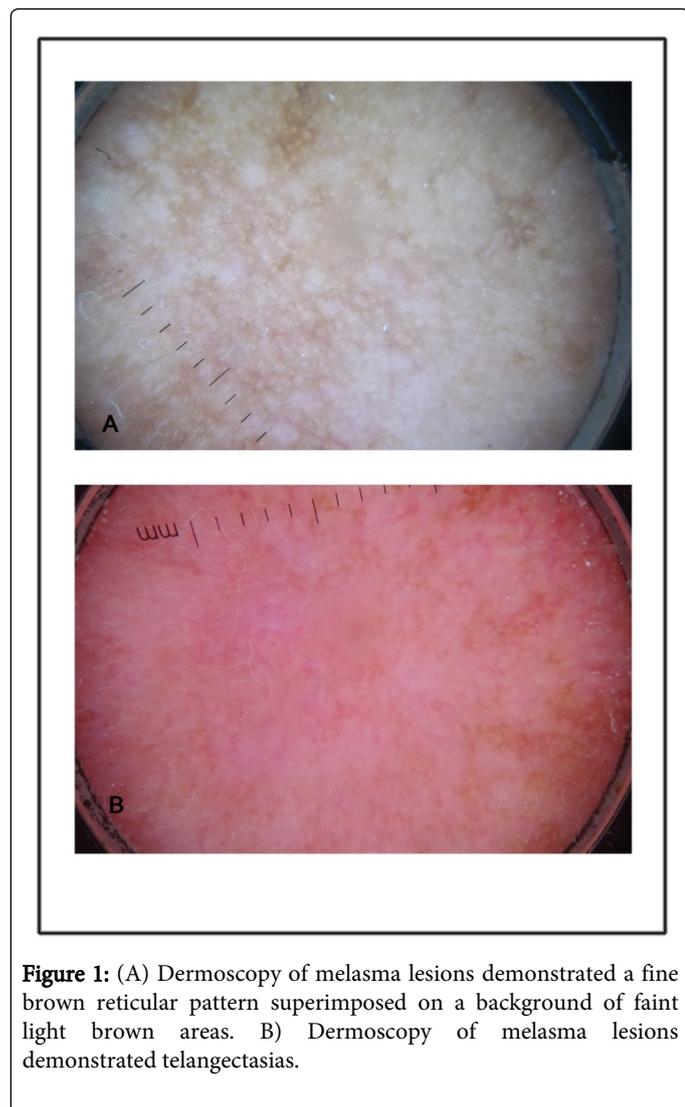
	Group A (n = 20)		Group B (n = 20)		Group C (n=20)		Total	
	No.	%	No.	%	No.	%	No.	%
Predisposing factors								
UVR	11	55.0	13	65.0	7	35.0	31	51.7
χ^2 (p)	3.737 (0.154)							
Pregnancy	11	55.0	6	30.0	9	45.0	26	43.3
χ^2 (p)	2.579 (0.275)							
Hormonal	10	50.0	12	60.0	12	60.0	34	56.7
χ^2 (p)	0.543 (0.762)							
Cosmetic	4	20.0	3	15.0	3	15.0	10	16.7
χ^2 (MCp)	0.240 (1.000)							
Family history	6	30.0	6	30.0	8	40.0	20	33.3
χ^2	0.600 (0.741)							
Fitzpatrick skin type								
III	5	25.0	5	25.0	8	40.0	18	30.0
IV	14	70.0	14	70.0	8	40.0	36	60.0
V	1	5.0	1	5.0	4	20.0	6	10.0
$^{KW}\chi^2$ (p)	0.047 (0.977)							
Pattern of melasma								
Centrofacial	16	80.0	14	70.0	16	80.0	46	76.7
Malar	3	15.0	4	20.0	3	15.0	10	16.7
Mandibular	1	5.0	2	10.0	1	5.0	4	6.7
χ^2 (MCp)	0.874 (0.922)							
Wood `s light								
Epidermal	8	40.0	9	45.0	13	65.0	30	50.0
Dermal	7	35.0	4	20.0	2	10.0	13	21.7
Mixed	5	25.0	7	35.0	5	25.0	17	28.3
χ^2 (MCp)	4.794 (0.337)							

Table 2: Comparison among the studied groups according to predisposing factors, Fitzpatrick skin type, Pattern of melasma and Wood `s light examination.

mMASI		Group A (n = 20)	Group B (n = 20)	Group C (n=20)	$^{KW}\chi^2$	P
before treatment	Range	5.40–13.40	7.20–16.80	5.40–17.40	1.520	0.468
	Mean \pm SD.	9.37 \pm 2.18	10.55 \pm 2.60	10.25 \pm 2.93		
after treatment	Range	4.30–12.0	1.0–14.40	1.50–12.40	3.204	0.202

	Mean ± SD.	7.51 ± 2.24	6.46 ± 2.75	6.19 ± 3.26		
% of change		€ 19.85	€ 38.77	€ 39.61		
Z		3.519*	3.825*	3.824*		
p		<0.001*	<0.001*	<0.001*		

Table 3: Comparison among the studied groups according to mMASI score before and after treatment.

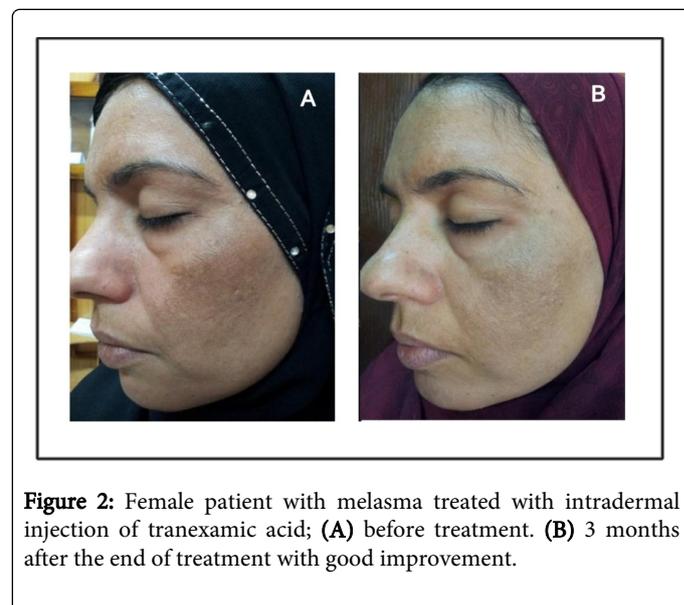


Regarding the response to treatment in the different studied groups, in group A; good response (Figure 2) was detected in 8 patients (40%), poor response was detected in 8 patients (40%) and no response was detected in 4 patients (20%). In group B; excellent response (Figure 3) was detected in 1 patient (5%), very good response was detected in 7 patients (35%), good response was detected in 5 patients (25%), poor response was detected in 6 patients (30%) and no response was detected in 1 patient (5%). In group C; excellent response was detected in 2 patients (10%), very good response (Figure 4) was detected in 7 patients (35%), good response was detected in 6 patients (30%), poor response was detected in 4 patients (20%) and no response was

detected in 1 patient (5%). There was a statistically significant difference between the studied groups as regard the response to treatment (p value=0.004*).

Efficacy	Group A (n=20)	Group B (n=20)	Group C (n=20)	KWχ2	P
Mean ± SD.	0.0-34.70	0.0-86.10	0.0-76.0	11.594	0.003*
Range	20.10 ± 12.15	39.24 ± 21.27	41.85 ± 22.17		
p1		0.004*	0.003*		
p2		0.675			

Table 4: Comparison among the studied groups according to efficacy of treatment.



Correlation between efficacies of treatment with age of patients revealed an inverse relation where the patients with younger age had higher efficacy of the treatment than the older in the different studied groups. Correlation between efficacies of treatment with duration of melasma revealed an inverse relation where the shorter duration of melasma had higher efficacy of treatment than the longer duration in the different studied groups. Correlation between efficacy of treatment with and Fitzpatrick skin phototype revealed an inverse relation where skin phototype III had higher efficacy than phototype VI than phototype V in the different studied groups (Table 5).



Figure 3: Female patient with melasma treated with topical silymarin cream; A) before treatment. B) 3 months after the end of treatment with excellent improvement.



Figure 4: Female patient with melasma treated with 50% glycolic acid peeling; (A) before treatment. (B) 3 months after the end of treatment with very good improvement.

	Efficacy							
	Group A		Group B		Group C		Total Sample	
	rs	p	rs	p	rs	p	rs	p
Age	-0.016	0.946	-0.215	0.363	-0.275	0.240	-0.134	0.306
Duration	-0.345	0.137	-0.238	0.313	-0.498*	0.025	-0.307*	0.017
Fitzpatrick skin type	-0.212	0.371	-0.093	0.697	-0.598*	0.005	-0.327*	0.011

Table 5: Correlation between efficacy of treatment with age of patients, duration of melasma and Fitzpatrick skin type in studied groups of patients.

There was a statistically significance difference as regard the relation between the efficacy and wood's light examination (p value=0.001*) in the different studied groups revealed that the highest efficacy was in epidermal type ($41.02 \pm 22.3\%$) followed by mixed type $34.56 \pm 17.60\%$ then dermal type ($15.82 \pm 10.0\%$). No significant association between response to treatment and vascular proliferation by dermoscopy of melasma was observed.

Regarding the side effects of the treatment in the different studied groups, in group A, there was burning pain and wheal at the site of injection in all patients and erythema in 5 patients (25%). In group B, no side effects were reported. In group C, post inflammatory hyperpigmentation was reported in 6 patients (30%) while no side effects in 14 patients (70%). There was a highly significant difference between group A and both (B and C) groups (p value<0.001*). So, groups B and C were more safe than group A. There was significant difference between group B and C as regards the side effects (p value=0.020*) where, group B was more safe than group C (Table 6).

Side effects	Group A (n=20)		Group B (n=20)		Group C (n=20)		χ^2	MCp
	No.	%	No.	%	No.	%		
No side effects	0	0.0	20	100.0	14	70.0	100.00*	<0.001*
burning pain	20	100.0	0	0.0	0	0.0		
Wheal	20	100.0	0	0.0	0	0.0		
Erythema	5	25.0	0	0.0	0	0.0		
Post inflammatory hyperpigmentaion	0	0.0	0	0.0	6	30.0		
p1			<0.001*		<0.001*			
p2			0.020*					

Table 6: Comparison between the studied groups according to the side effects of treatment.

Discussion

Melasma, though benign, can be extremely psychologically distressing and has been shown to have a significant impact on quality of life, social, and emotional wellbeing [2]. There is no universally effective specific therapy [7], and no single therapy has proven to be of benefit to all patients as the sole therapy, combinations of modalities can be used to optimize management in difficult cases [9]. So, the aim of this study was to evaluate and compare the efficacy of intra-dermal injection of tranexamic acid, topical silymarin cream and glycolic acid peeling in treatment of melasma.

In the present study; regarding the efficacy of treatment, there was a highly statistically significant difference in mMASI score after treatment among the three studied groups. Group C showed the highest efficacy, followed by group B and the least efficacy was in group A. These results were in consistent with Javaheri et al., 2001 [10] who studied the efficacy of glycolic acid peel 50% monthly for 3 months with prepeel treatment with 10% glycolic acid lotion; they reported that, there was significance decrease in MASI score from the base line to the end of the treatment. A dose-response trial studying

the effect of varying concentrations of glycolic acid peels for melasma showed that 52.5% glycolic acid applied for 3 minutes led to clinical improvement [11]. Topical application of glycolic acid at concentrations of 40% and 50% had resulted in decrease of melanin deposits in the epidermis as well as acceleration of desquamation [12]. The difference between our results than other studies may be because in the current study we used the glycolic acid peel only without any other combinations while other studies used combination treatment with glycolic acid peeling.

The beneficial effect of glycolic acid is due to it is the smallest in molecular weight of the alpha hydroxyl acids which become more active and penetrates the skin more deeply [10], diminishes corneocyte adhesion in the upper layers of the epidermis, causing an epidermolytic effect [13], facilitating the removal of melanized keratinocytes, leading to melanin pigment loss and acceleration of skin turnover [5]. GA directly inhibits melanin formation in melanocytes as well [14].

In group B, there was a highly significance decrease in mean mMASI score from the base line to the end of the treatment. These results agreed with Altaei [4]. The beneficial effect of silymarin is due to its ability to reduce and suppress harmful effects of solar UV radiation, such as UV induced oxidative stress, inflammation, edema and DNA damage as well as induction of apoptosis [15]. Silymarin shows strong free radical-scavenging activity. It inhibits lipid peroxidation and provides significant protection against UVB induced depletion of catalase activity. Therefore, silymarin can effectively terminate the harmful biochemical reactions by scavenging free radicals and reactive oxygen species (ROS), and by strengthening the cellular antioxidant status [16]. Silymarin inhibited L-DOPA oxidation activity of tyrosinase and decreased the expression of tyrosinase protein due to the suppression of PGE-2 production [17]. Silymarin suppresses the production of interleukin-1b (IL-1b) and prostaglandin E2 (PGE-2) produced by cyclooxygenase-2 (COX-2) and also tumour necrosis factor- α (TNF- α) [18], decreased nitric oxide synthase (iNOS) and COX-2, as well as nuclear factor kB (NF-kB) [19]. Thus, it would appear that the anti-melanogenesis activity of silymarin might be related to its anti-inflammatory effect [17].

In group A, there was highly significance decrease in mMASI score from the base line to the end of the treatment. These results were in agreement with Lee et al., [3] who used intradermal injection of 0.05 ml of tranexamic acid 4 mg/ml in patients with melasma weekly for 12 weeks and they reported a significance decrease in mean MASI score. In agreement with our study, Ayuthaya et al. [20] studied topical 5% tranexamic acid twice daily for 12 weeks for the treatment of epidermal type melasma in split face trial study.

Tranexamic acid inhibits UV-induced plasmin activity in keratinocytes by preventing the binding of plasminogen to the keratinocytes results in less free AA and a diminished ability to produce PGs, and this decreases melanocyte tyrosinase activity [21]. Plasmin also participates in the release of basic fibroblast growth factor (bFGF), which is again a potent melanocyte growth factor [22]. Tranexamic acid suppresses angiogenesis, and also inhibits neovascularization induced by (bFGF) and decrease mast cells as it plays an important role in development of melasma [23]. In 2010, Li et al. used intradermal TA on guinea pigs, which had been exposed to UVB for 1 month. Injection was performed every day for another month. They found that at the basal layer of exposed epidermis, the number of melanocytes was not reduced, but the melanin content was

significantly lowered. Hence, they suggest TA has no effect on the number of melanocytes, but on the expression of melanin [24].

Regarding the side effects in our study, they were more reported in group A followed by group C while no side effects were reported in group B. These results were in agreement with Lee JH et al. [3] who reported that there were burning pain and wheal at the site of injection in all patients (100%). While Ayuthaya et al. [20] reported that there was minor irritation in (9.5%) due to treatment with topical tranexamic acid. In group B, no side effects were reported in all patients. These results agreed with Altaei [4] as she reported that there were no local or systemic side effects. In group C, there was post inflammatory hyperpigmentation which have been reported in 6 patients (30%) and no side effects in 14 patients (70%).

It could be concluded that silymarin cream was a novel, effective and safe treatment modality for melasma especially in epidermal and mixed types in Fitzpatrick skin phototype III, IV and V as it showed a significant reduction of pigment and melasma lesion in a short period of time. It was as effective as 50% glycolic acid peeling in the treatment of melasma without post inflammatory hyperpigmentation that occurred by glycolic acid peeling.

The intralesional localized microinjection of tranexamic acid was a new therapeutic modality for the treatment of melasma but it was less effective than silymarin cream and 50% glycolic acid peeling.

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