TRANEXAMIC VERSUS KLIGMAN IN MELASMA TREATMENT

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ABSTRACT

Melasma is a common dermatological condition that may presents a great therapeutic challenge to treat. The specific aim of the present study was to evaluate the efficacy and safety of topical tranexamic Acid **(**TA 3 %) loaded chitosan microparticles (TA-CsMPs) as compared with modified Kligman's formula. A total 24 females with melasma in our nonrandomized comparison study were classified into 2 groups. Group (I) females advised to apply topical 3 % TA-Cs microgel twice daily, while group (II) was received Kligman regimen once daily at night. A modified Melasma Area Severity Index (m-MASI) score was used to evaluate patients clinically once weekly for 6 weeks and followed up for 3 more months after treatment completion. Dermal type of melasma, with a lateral or centro-facial pattern of distribution and Fitzpatrick type III was found mostly in patients. The m-MASI score was significantly lower in comparison to the baseline in both investigated groups. Beside the adverse reaction as redness, irritation, or burning associated with topical Kligman formula, TA-CsMPs regimen has superior efficacy and safety in melasma treatment. Taken together, our current outcomes demonstrated that topical 3% TA-CsMPs is an innovative, effective, and could be a potentially promising safe alternative with good patient acceptance for melasma treatment.

KEYWORDS: Melasma, Tranexamic acid, Chitosan microparticles, MASI score.

INTRODUCTION

Melasma (chloasma or pregnancy mask) is an acquired hypermelanosis disproportionately affects people of Asian, African, and Hispanic descent. Melasma is characterized by hyperpigmentation on sun-exposed facial skin, especially the cheeks, forehead, chin, upper lip and supralabial Regions [1]. Melasma is commonly seen in females than in males with prevalence of 40 % and 20 %, respectively [2]. The pathogenesis of melasma is still unclear, however ultraviolet radiation often combined with genetic, and hormonal factors are the major melasma-related pathological factors. one theory suggested that ultraviolet light increases plasmin activity in keratinocytes, which

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leads to an increase the number of mast cells that in turn stimulates α melanocyte stimulating hormone which increase melanogenesis, so increase melanin content and increase vascularization by vascular endothelial growth factor, which increase melanocyte proliferation and migration [3].

Based on Wood's lamp evaluation, and depending on the depth of pigment deposition, melasma is divided into four histological types: epidermal, dermal, mixed, and telangectatic type melasma [4].

In spite of various treatment arms, melasma is still challenging because it is often recalcitrant to therapy, especially in the dermal type, and it frequently recurs even after successfully cleared. Different treatment modalities such as topical therapy, systemic therapy and various procedural therapeutic options have been utilized in different studies with varying but less satisfactory outcomes [5].

Traditionally, the mainstays of treatment for melasma have been topical bleaching agents and strict photoprotection. Additional adjuvant treatment modalities include chemical peels, dermabrasion, and laser treatments, all of which have demonstrated limited efficacy [6].

Although, Kligman formula composed of hydroquinone 5%, tretinoin 0.1% and 1 % hydrocortisone, is the corner stone of epidermal melasma treatment [4].

Recently, there has been an interest in studying the effects of tranexamic acid (TA) in melasma.

TA is a synthetic derivative of amino acid lysine. It has been hypothesized that TA is a fibrinolytic agent with antiplasmin properties that can inhibit the release of paracrine melanogeic factors that normally act to stimulate melanocytes [6]. TA has been evaluated for the treatment of melasma in various formulations, including topical, intradermal, and oral. Unfortunately, the high potential of TA for melasma treatment is hampered by its low skin permeation and deposition.

Numerous approaches have been made to ameliorate the skin permeation of topical TA by loading in nano and microscale system. Chitosan is a biodegradable, biocompatible cationic polymer with low toxicity, and adhesive properties, which has the ability to enhance the penetration of large molecules across mucosal surfaces. Chitosan can be used to obtain nanoparticles or microparticles as a vehicle for the encapsulation of active ingredients. Chitosan based microparticles are very promising for delivering drug to the dermis layer via barriers of the stratum corneum, because of their ability to improve medication water solubility, bioavailability, and antiplasmin activity.

Despite our advances with technology and new formulations of medications, treatment of melasma remains challenging. So, our goal in the current study is to be proven that topical TA loaded chitosan microgel has begun to show more promise for the treatment of melasma.

SUBJECTS AND METHODS

In the current nonrandomized controlled study, 24 female patients who fulfilled the criteria for inclusion were recruited and conducted in the outpatient clinics of dermatology, venereology and andrology department, Zagazig University Hospitals, Zagazig City, Sharika

Governorate, Egypt, for a period of eight months from February 2019 till July 2020. Inclusion criteria: young, aged women 20 - 58 years old who had facial melasma however mild, moderate, or severe, with all types (epidermal, dermal, or mixed).
Exclusion criteria: Females on any current melasma medication, patients Utilizing any topical melasma treatment one month before, or hormonal contraception, pregnancy or breastfeeding females, or patients with thrombocytosis.

METHODOLOGY

The suggested protocols were declared to all participant who met the inclusion criteria before the beginning of the study. Approval of the study design was obtained from the Institutional Review Board (IRB) unit, and by the Research Ethical Committee in the faculty of Medicine, Zagazig University (IRB); (ZU-IRB#4911#14/10/2018).
The suggested study protocols were conveyed to all participants, a verbal and an informed written consent document was signed by those who agreed to participate before treatment regimen.
After receiving patient consent from all-women to participate in our current study, all patients were subject to the following:
History taking: Personal (name, sex and age). Pregnancy, sun exposure, past history of any systemic diseases as coagulopathy, thyroid disease, and so on. Family history of melasma. Present history that included onset, course, duration.
Previous history of melasma treatment such as chemical peeling, meso-therapy, Laser or whitening creams, together with history of treatment outcome, complications and recurrence post treatment.
Dermatological examination: The skin photo type, severity and melasma type were assessed using an m-MASI scoring method that computed by subjective evaluation of 2 parameters: darkness (D) and involvement area (A), as reported early by (Pandya et al., 2010) as illustrated in figure (1). Based on colour and pigmentation position that clinically assessed using Wood's lamp examination, melasma was histological categorized into epidermal, dermal, or mixed types.
Clinical assessment: using a Canon digital camera (IXUS 160), a digital facial color photographs of the anterior, right and left profile were taken every week through treatment period (for 6 weeks) and three months post-treatment for follow up. Using a modified MASI scoring technique, our study outcomes were assessed at day 42 of the treatment period. Additionally, any noticed side effect as well as Patient satisfaction were recorded.
Treatment:
Preparation of TA loaded Chitosan microparticles (TA-CsMPs) was prepared in National Research Centre at Cairo, TA-CsMPs by using the methods of emulsification and crosslinking with sodium alginate (Na. Alg) as early described by. Gel formulation was prepared by dispersing 1.5 % w/v hydroxy methyl cellulose (HPMC) into known quantity of deionized water, continuously stirring at 800 rpm followed by addition of 0.02% w/v sodium methyl paraben and was stirred for additional 30 min. 3% w/w TA-CsMPs then was dispersed in

appropriate quantity of polyethylene glycol and later dispersed in HPMC gel bases while stirring at 800 rpm followed by further agitation for 30 min to obtain microgel.

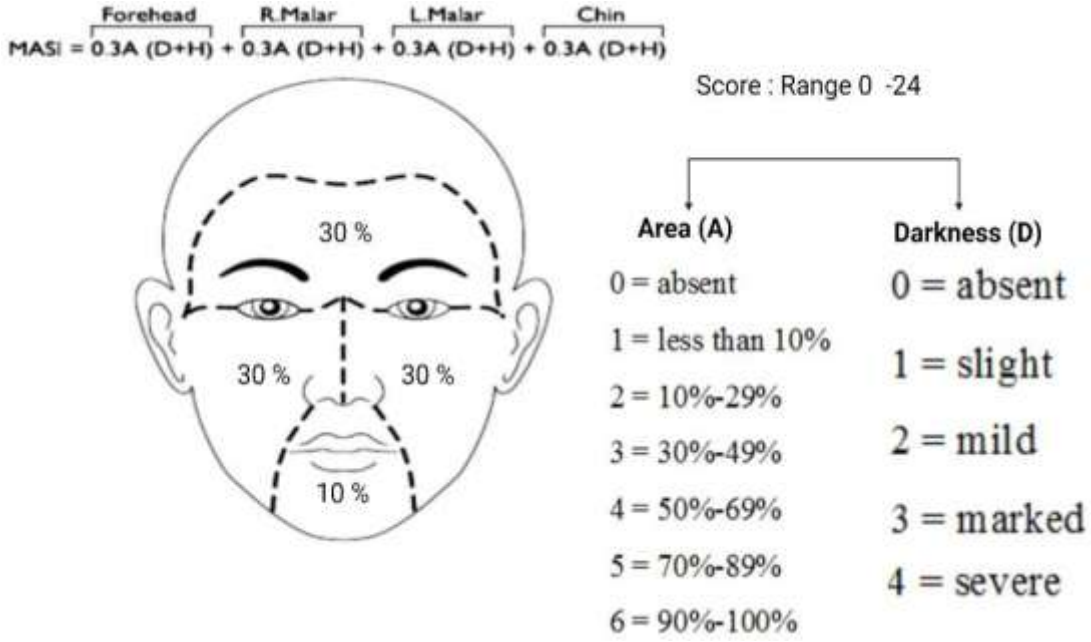

Figure (1): The new modified MASI score (Pandya et al., 2010).

Preparation of kligman formula:
Trituration of mometasone furoate 0.1%, tretinoin 0.025%, and hydroquinone 2% cream in wide open jar. Levigating of vitamin C powder in quantity sufficient of propylene glycol and dispersed in cream combination while stirring as antioxidant to avoid oxidation of hydroquinone and darkness of the preparation. Possible side effects (as pain, erythema or burning sensation) after product application were explained. Strictly, sunscreen was used throughout study period and afterwards. To avoid unrealistic expectations, each participant was asked about her goals, concerns, and expectations about the treatment. Study design: According to the study protocol, a total of 24 female melasma patients were enrolled. The population volunteers were nonrandomly allocated into two categories of treatment: -
Group I (12 female cases): received one mg of 3% TA-CsMPs topically applied at melasma site every 12 hour/day for 6 weeks. Group II (12 female cases): received modified kligman formula applied topically at melasma site once per day in dark room at night, left for 30 min followed by facial wash. Both Categories were evaluated every week for 6 weeks and follow up 8-month post treatment.
Therapeutic response: The degree of improvement was categorized as follows; (1) no response: no improvement, (2) mild response: < 25% improvement, (3) moderate response: 25% to < 50% improvement, (4) good response: 50% to < 75% improvement, (5) very good response: >75% improvement. Each case was followed

up for 8 months to look for further improvement/relapse [8].

Patient satisfaction: At the end of treatment, upon patient's questioner reports, the degree of improvement was categorized as very good >75%, good 50% to < 75%, moderate 25% to < 50%, and mild < 25% improvement (Saleh et al., 2019).

Side effects: during treatment, any noticed erythema, discomfort or burning sensation was being recorded as adverse treatment regimen.

Statistical Analysis: - Gathered data during the history, dermatological examinations, basic clinical investigation, and result evaluations were coded and analyzed with Microsoft Excel software. For analysis, data were then entered into the SPSS version 20.0 (Statistics Package Social Science, SPSS Inc., Chicago, IL), USA. Chi square test (X2) was applied to estimate qualitative variable difference and association, whereas ANOVA or Kruskal Wallis was used to calculate the differences between quantitative independent multiple groups. Paired nonparametric t-test was used to calculate P value in each group (It was thought that $P < 0.05$ was significant).

Table (1): Participants' clinical data characteristics and distribution among studied groups

	Group (I) (N = 12)		Group (I) (N= 12)		Test	P-value
	Number	%	Number	%		
Age (year) Rang	38.83 ± 4.13 35 to 42		38.5 ± 4.23 36 to 47		0.03 22 □	0.9 67 (NS)
Risk Factors						
Contraceptive	1	8.3%	3	25 %	9.445‡	0.5 01 S)
Family +VE	1	8.3%	0	0		
Drugs	3	25 %	0	0 %		
Idiopathic	0	0 %	2	16.7 %		
Pregnancy	4	33.3%	0	0 %		
Sun exposure	3	25 %	7	58.3 %		
Co-morbidities						
No	9	75 %	9	75 %	0.321*	0.8
Yes	3	25 %	3	25		
Drugs						
No	7	58.3%	7	58.3%	5.561*	0.0
Yes	5	41.7%	5	41.7%		(NS)

‡ = Fisher exact * = Student T-test

RESULTS

A total of 24 diagnosed melasma females had been involved in the current study, with mean age of 38.83 ± 4.13, and 38.5 ± 4.23 for group group (I) & (II), respectively. There was a none -

significant difference reported between both groupscategories as dedicated in Table (1). In addition, regarding clinical character of all participants, there was non-significant difference or association (P > 0.05) among the two studied groups. Our study revealed that sun exposure was the most common cause of melasma among all female patients; in seven (58.3 %) cases, followed by pregnancy in four (33.3%) cases, then oral contraceptive pills in one (8.3 %) cases, and family history, as illustrated in Table (1).

Regarding melasma distribution patterns, skin phototype, melasma type and lesion duration as shown in Table (2), there was no statistically significant change (P > 0.05). Based on Wood's light examination, our research outcomes revealed that the most common melasma type was the dermal type, Table (2). A total of 12 cases (50 %) with equal distribution among the two categories (6 cases in each group). According to the region involved, majority of cases (8 in group I and 4 in group II) had Lateral lateral type of melasma followed by centro-facial and malar types. While the majority of the cases (50%) had Fitzpatrick III skin with a non-substantial difference between the two studied categories, P =0 .68, Table (2).

Table (2): Melasma distribution patterns, skin phototype, type and duration of melasma

	Group (I) (N = 12)		Group (II) (N= 12)		Test	P-value
	Number	%	Number	%		
Fitzkpatrick type						
II	3	25 %	1	8.3 %	3.91 # 0.68 (NS)	
III	6	50 %	6	50		
IV	3	16.7 %	4	33.3 %		
V	0	0.0 %	1	8.3 %		
Pattern of disease						
Central	0	0 %	0	0 %	7.51 #	0.306
Type of lesion						
Dermal	6	50 %	6	50 %	3.615 #	0.624 (NS)
Epidermal	5	41.7 %	4	33.3 %		
Mixed	1	8.3%	2	16.7 %		
Duration of lesion						
Mean ±SD	4.5 ± 2.02		4.18 ±1.27		F value =2.481 □	0. 0998 (NS)

X2 = Chi square □ = ANOVA

A m-MASI score was recorded in all 24 cases at base line pre and sex week post treatment. 12 women were received topical TA-Cs microgel while the remaining 12 cases of group II were given modified kligman's formula.

Our results showed that there was no-significant change in the mean m-MASI score recorded at baseline pre-treatment between the 2 studied groups, p > 0.05.

Table (3) revealed that in comparison to pre-treatment evaluation, a significant reduction in mMASI score (p = 0.004), to reach 2.4 ± 1.32 and 2.822 ± 1.623 for treatment (I, TA-CsMPs) and treatment (II, kligman's formula) six weeks post-treatment. The mean m-MASI score was decreased in both studied groups, indicating that the both topical treatments regimen had a significant improvement during the study period and were effective for melasma treatment, (1 and 2), with more significant improvement and rapid reduction in TA-CsMPs treated group.

Table (3): MASI score distribution before and after treatment among studied groups

	Group I	Group II	Test	P
MASI score at 0 weeks Before treatment	5.23 ± 2.3 5.1 (1.8 - 9.6)	5.693 ± 2.092 5.7 (2.9 - 9.1)	+ 2.3512	0.146
MASI at 6 weeks after treatment	2.4 ± 1.32 # 4.75 (1.2 - 12.0)	2.822 ± 1.623 2.25 (0.6 - 5.70)	+ 6.443	0.004*
P (paired t-test)	0.003*	0.001**		
Percentage of change	54.12 ± 14.52#	50.72 ± 15.63	14.256	0.001**

MASI = Melasma Area and Severity Index + = Kruskal Wallis

Regarding patients satisfaction, therapeutic outcome, complication occurrence or recurrence of melsama, we found a non-significant difference between both treatment, Table (4). The patients' satisfaction of melasma improvement was evaluated during 6 weeks of treatment. At the end of 6th week, 16.7 % of the cases showed very good response in each treatment group, while about of 41.7 % of cases in TA-CsMPs showed moderate response and good responses were seen by 41.7 % in Kligman's formula treated group, Table (4).

Interestingly, all treated cases in group I showed no adverse effect, while these adverse reactions were more seen in kligman's formula treated group, ~16.7 % of the cases showed pain, and 8.3 % showed redness. Overall, a significant reduction without any adverse reaction was noted more in TA-CsMPs treated cases, but adverse effects were more pronounced in Kligman's formula treated group.

DISCUSSION

Melasma is a common chronic pigmentary skin disease that commonly affects African, Hispanic, Latin, Indian, American, Asian racial groups and areas with intensive sun exposure [9]. The disorder is more seen in females than in males particularly women in reproductive age especially who have skin phototypes IV and V [2]. Histologically, melasma are epidermal, dermal, mixed or telangectatic type which identified using wood's light test. Epidermal melasma appears as dark brown in color, while in dermal melasma, there is greyish blue pigmentation which did not show accentuation by using wood's light examination. Mixed type is the most

Table (4): Therapeutic response, women satisfaction, Side effects and recurrence distribution among studied groups.

	Group I		Group II		Test	P-value
	No.	%	No.	%		
Therapeutic						
No response	0	0	0	0	++ 8.47	0.38
Mild	2	16.7	1	8.3		
Moderate	5	41.7	4	33.3		
Good	3	25.0	5	41.7		
Very Good	2	16.7	2	16.7		
Satisfaction						
Mild	2	16.7	1	8.3	++ 10.2	0.11 (NS)
Moderate	5	41.7	4	33.3		
Good	3	25.0	5	41.7		
Very Good	2	16.7	2	16.7		
Complication						
No	12	100	9	75	# 6.54	0.16
Pain	0	0	2	16.7		
Redness	0	0	1	8.3		
Recurrence						
Yes	10	83.3	6	50.0	# 3.0	0.22
No	2	16.7	6	50.0		
Time of recurrence	3.5 ± 0.7 #		2.33 ± 0.81		F = 4.94	0. 036*

X2 = Chi square ++ X2 Fisher exact

common, in which combined of dark, light brown pigmented patches.
If the area of involvement is considered it may be malar, centro-facial, oromandibular.
From etiological point of view, pigmentation is ultimately caused from melanin over production by pigment cells (melanocytes); which is then taken either by epidermal melanosis (keratinocytes) and/or dermal melanosis (deposited in the dermis). UV light is thought to cause reactive oxygen species (ROS), through activating nitric oxides and increasing melanogenesis [6]. Furthermore, hormonal therapy, genetic abnormality, pregnancy, and oral contraceptives pills, hormone therapy, are also etiological contributing factors [10]. Melasma imparts a harmful social interaction with a low living quality, and emotional well-being [11]. There is a continuing need for innovative medical strategies for melasma treatment.
Different medical approaches have been suggested and used in melasma. Oral modality includes tranexamic acid [10]. Topical modalities include modified Kligman's formula, kojic acid, glycolic acid and silymarin cream.
The gold stander topical treatment modality is Kligman's formula, but burning sensation, pain and redness of hydroquinone is hampered its use for prolonged periods of time. Furthermore, disagreeable adverse effects of topical corticosteroid as atrophy, acneiform eruptions, and hypertrichosis discounted the topical application on the face for long time [12].
TA is a synthetic derivative of amino acid lysine, that regulates and reduces haemostatic fibrin dissolution. TA has been extensively investigated as a potential agent for melasma treatment and recently received a great attention as skin-lighting agent. It has been evaluated for the treatment of melasma in various formulations, including topical [3], intradermal, and oral [13].
It has been hypothesized that TA is a plasmin inhibitor can inhibit the release of paracrine melanogenic factors that normally act to stimulate Tranexamic acid is a plasmin inhibitor. Also, it inhibits UV induced plasmin activity in

keratinocyte by preventing the binding of plasminogen to keratinocyte, which results in a less free arachidonic acid and diminished ability to produce prostaglandin (PGs) and subsequently reduces melanogenesis in melanocyte.
Our clinical research aims to evaluate the effectiveness and safety of topical 3% TA-Cs microgel versus Kligman formula in melasma treatment. Twenty-four females with different melasma types, a variety of skin phototype, and lesion distribution pattern were included in our study. Baseline MASI score was calculated pre and 6th weeks post-treatment using topical application of TA-Cs microgel (group I) and Kligman formula (group II).
As demonstrated in Table (1), there were no statistically significant changes among the two treatment groups regarding age or risk factors. Based on wood's lamp evaluation, the majority of females who took part in the current study have latral type of melasma, and according to distribution pattern, lateral type of melasma with Fitzpatrick skin type III (50 %) was the most common. These results were in line accordance with the results reported by Momin et al., 2020 who found that 65.2 % patients were having Centro-facial type of melasma and also, with another study done by Budamakuntla et al also, major clinical pattern was centro-facial seen ~ 63.8 % of cases [8].
In our study we found superior result in TA-CsMPs regimen (group I) with 2.43 of more reduction as compared to Kligman formula treated group (1). In group II, mean m-MASI score at day 0 was 5.23 ± 2.3, which decreased to be 2.4 ± 1.32 at day 42 after treatment. While in group I, mean base line m-MASI score was 5.693 ± 2.092, and reached to 2.822 ± 1.623 at the completion day of study period (day 42). These results are consistent with more recent study reported by Saki et al., 2020 who showed 0.98 reductions of MASI score in intradermal TA injection group vs to topical hydroquinone after four weeks of treatment.
In this study, although there was no significant difference between both treated groups, patient satisfaction was higher in TA loaded chitosan microgel. Also, regarding occurrence or recurrence time, there was no-significant difference among the two studied groups but recurrence time was significantly longer in TA-Cs microgel groups due to sustained release action of microparticlws [14].
Our present outcomes agreed with [10] who found that irrespective of the used treatment regimen, relapses are known to occur in melasma, so that a safer modality could be used repeatedly, is always desirable.
A comparative study of topical 5% tranexamic acid and Kligman formula was done on 25 patients was reported by Khuraiya et al., in which equal result was achieved in both groups with lesser side effects but delayed response was achieved in topical 5% TA group and showed a potential newer alternative of modified Kligman regimen group. This finding was somewhat comparable to our study [15].
Another comparative study was done by Momin et al., who aimed to compare the efficacy and safety of topical tranexamic acid versus topical modified kligman regimen on 46 patients. 72.9 % and 84.78% improvement in mean MASI score was seen respectively at the end of

6 months which demonstrated that modified kligman regimen gives better result compare to topical tranexamic acid [16].

CONCLUSIONS

The result of our study revealed that both topical tranexamic acids loaded chitosan nanogel and Kligman's formula was effective in the melasma treatment. However topical Kligman's formula is better than topical tranexamic acid, but the latter is a safer alternative to initiate the melasma treatment. Further studies are needed for the treatment of melasma with a large sample and more duration. Taken together, our current outcomes demonstrated that topical 3% TA-CsMPs is an innovative, effective, and could be a potentially promising safe alternative with good patient acceptance for melasma treatment. Further studies with different treatment modality are needed to be investigated on large population sample for long duration period.

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