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Original Research Article

Evaluation of therapeutic efficacy of tranexemic acid compared to kligman formula in the management of melasma

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ABSTRACT

Introduction: Facial melanoses (FM) are a common presentation in Indian patients, causing cosmetic disfigurement with considerable psychological impact. Melasma is an acquired non-inflammatory hypermelanosis of multifactorial etiology with significant cosmetic deformity. Different treatment modalities have been utilized in different studies with varying outcomes. Recent clinical trials with Tranexamic acid are promising.

Objective: To compare the therapeutic efficacy of Tranexamic acid (TXA) in 2 different modalities with Modified Kligman formula in the management of melasma.

Materials and Methods: This is a prospective, randomised, open-label study with a sample size of 45 patients of melasma fulfilling inclusion and exclusion criteria were randomly divided into 3 groups, 15 in each group. Group A: At home, daily applicatioin of modified kligman formula at night for 3 months. Group B: 12 sittings of microneedling followed by Tranexamic acid application was done weekly. Group C: 12 sittings of intralesional tranexamic acid (4mg/ml) was done weekly. Clinical images and dermoscopic images were taken at each visit including modified Melasma Area Severity Index (MASI) scoring, patient global assessment and physician global assessment to assess the clinical response.

Results: Modified kligman formula group showed 42% improvement in MASI score by the end of 12 weeks, where as intralesional Tranexamic acid group showed 36% improvement followed by 30% improvement in microneedling with Tranexamic acid group. When statistically compared with Analysis of variance (ANNOVA) test, there was no significant difference ($p=0.62$) between three groups. But in individual groups there was significant difference ($p<0.05$) in MASI at 0 weeks and 12 weeks. Dermoscopic images showed perilesional hypopigmentation and telangiectasias with modified kligman formula, which was not seen with Tranexamic acid. Patient assessment score revelaed satisfaction with modified kligman formula in view of home application and pain during microneedling and microinjections which was not there in this group.

Conclusion: Modified kligman formula is found to be superior in the treatment of melasma, because of the synergistic activity of its components. But it has its own demerits of long term usage. Hence, Tranexamic acid which showed comparable results with kligman formula can be used either as a primary modality or as an adjuvant supportive therapy for maintanence.

1. Introduction

Melasma, a common form of acquired non-inflammatory hyper pigmentation is important, because it involves face in

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cosmetically conscious age group and significantly affects a person's psychological and social well being, contributing to lower productivity, social functioning and self-esteem.[1] It affects individuals of all races and both genders, and is observed in women of childbearing age and with darker skin types (fitzpatrick's IV-V) who live in areas with high ultraviolet (UV) radiation.[2–4]

The precise cause of melasma remains unknown. Multiple etiological factors are implicated, such as exposure to ultraviolet radiation, pregnancy, contraceptive pills, hormone replacement therapy, cosmetics, phototoxic and anti-seizure medications.[3] In addition to the UV light itself, photo-induced hormones, growth factors, and chemical mediators of inflammation, which influence the function of melanocytes directly or indirectly, might contribute to the UV-induced pigmentation.[5]

Depending on the location of melanin, melasma is classified into:[6]

1.1. Epidermal type

In which the pigment is brown and margins of the lesions are well defined and geographical.

1.2. Dermal type

In which the pigment is grey-brown and the margins of the lesions are poorly defined.

1.3. Mixed or epidermo-dermal type

In which melanin is present both in epidermis and dermis.

1.4. Indeterminate type

In which it is difficult to classify melasma, even with Wood's light as melasma in dark skinned individuals.[7]

Based on distribution on face, three patterns of melasma are recognized:

1.5. Centrofacial

Most frequent (63%) pattern with pigmentation on cheeks, forehead, upper lip, nose & chin.

1.6. Malar

Constituting 21%, with pigmentation present only on cheeks and nose.

1.7. Mandibular

Least common (16%) type with pigmentation on ramus of the mandible.

Depending on the natural history of the lesions, melasma may also be classified into:

1.8. Transient type

Which disappears within a year of withdrawal of hormonal stimulus.

1.9. Persistent type

Which persists for more than a year after withdrawal of hormonal stimulus and is maintained by UVR and other factors.

Due to its high prevalence and psychological impact, many studies have been conducted regarding the therapeutic options for melasma. Different treatment modalities such as topical depigmenting agents,[8,9] chemical peels,[10] dermabrasion and laser therapies[11] have been utilised in different studies with varying outcomes.

The results of recent clinical trials using localized intradermal microinjections of tranexamic acid (TA)[12] and transepidermal delivery of TA using microneedling[13] in the treatment of melasma are promising.

The aim of this study was to evaluate the efficacy and safety of tranexamic acid and to compare its therapeutic efficacy with that of Modified Kligman formula, which is gold standard for melasma.

2. Materials and Methods

This is an open labeled, prospective, randomized, comparative study done on 45 clinically diagnosed melasma patients attending outpatient Dermatology, venereology & leprosy (DVL) department from January 2015 to May 2016. Patients between 20-50 years and both sexes were included in the study.

Patients with known hypersensitivity to Modified Kligman′s formula and Tranexamic acid, History of herpes simplex viral infection, Concurrent active disease to facial area (i.e. acne), History of abnormal wound healing, abnormal scarring & bleeding disorders, Pregnant/lactating females were excluded.

2.1. Ethical aspects

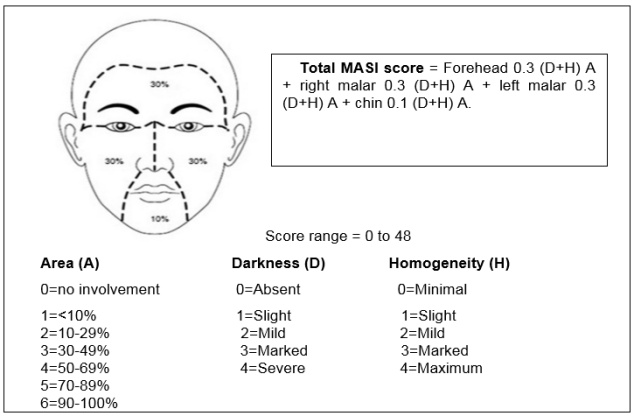
This study was conducted with prior approval from Research Ethics Committee and was done according to standards of good clinical practice. All patients signed an informed consent.

2.2. Methodology

All patients enrolled in this study were instructed to avoid sun exposure, use broad spectrum sunscreen during

day time and avoid melasma precipitating drugs like oral contraceptives.

After obtaining detailed personal and medical history, Wood's lamp examination was performed to classify the type of melasma. MASI scoring system was used to assess the severity of melasma.



All patients were randomly categorized into 3 groups, with 15 patients in each group.

Group A individuals were advised to apply modified kligman formula (2% hydroquinone + 0.025% tretinoin + 0.1% mometasone) at home daily at night for 12 weeks. They were advised to come for review every month.

For Group B individuals, topical anesthesia (EMLA) was applied for 45 min and then using hand held dermaroller with 192 needles of 1.5mm needle length was rolled over the affected area in all directions(vertical, horizontal and diagonal) and then 4mg/ml of Tranexamic acid was applied over rolled areas.

Tranexamic acid (Trapic) 100mg/ml is available as 5ml ampoule. 1ml was taken and diluted with distilled water to get a concentration of 4mg/ml, which was used in this study. The procedure was repeated weekly for 12 weeks.

For Group C individuals, intralesional Tranexamic acid 4mg/ml was given at 1cm intervals upto a maximum of 8mg/ml over the lesional area. The same was repeated weekly upto 12 weeks.

After every 4 weeks, clinical photograph and dermoscopic image was taken and MASI score was calculated for every individual. Patient assessment scoring was also noted.

Table 1:

Improvement	Grade	Score
<25%	Poor	1
25-50%	Fair	2
50-75%	Good	3
>75%	Excellent	4

3. Results

The Kruskal–Wallis (nonparametric ANOVA) test was used to compare the means of MASI scores before and after treatment in individual groups. The unpaired t-test with Welch correction was used to compare means of MASI scores between the 1^{st} and 2^{nd} group & 1^{st} and 3^{rd} group.

Out of 45 patients in this study, 2 were males (4.4%) and 43 were females (95.5%), majority were in the age group of 31-40 years (64.44%).(Table 2)

Table 2: Age & sex distribution

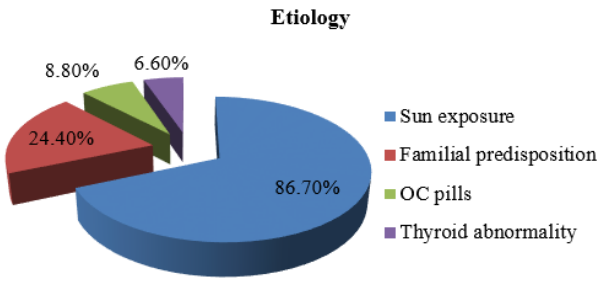
Age in years	Males	Females	Total	Percentage
21-30	1(2.22%)	9(20%)	10	22.22%
31-40	1(2.22%)	28(62.22%)	29	64.44%
41-50	0	6(13.33%)	6	13.33%
Total	2(4.44%)	43(95.55%)	45	

Majority of the patients had centofacial melisma (53.3%), followed by malar type (46.6%) and on woods lamp examination majority had epidermal melisma (48.8%), followed by dermal type (26.6%) and then mixed type (24.4%).(Table 3)

Table 3: Types of melasma

Types of melasma	Epidermal	Dermal	Mixed
Centrofacial	7	10	7
Malar	15	2	4
Total	48.8%	26.6%	24.4%

Various etiological factors involved are sun light (86.7%), familial predisposition (24.4%), OC pills (8.8%), thyroid abnormality (6.6%).Graph 1



Graph 1:

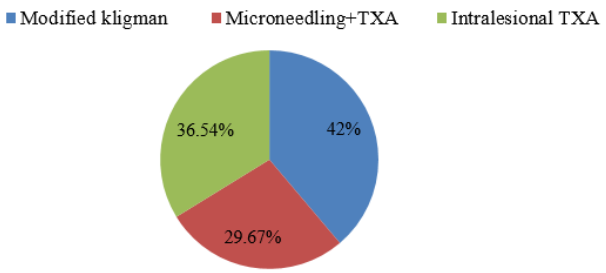
The total MASI in group A regressed from 105.9 to 65.5, in group B from 156.3 to 112.1 and in group C from 97.2 to 61.4 by the end of 12 weeks.

When mean MASI (± sd) was compared, in group A it regressed from 7.06±6.5 to 4.3±4 with 42% improvement,

in group B it regressed from 10.42±8.3 to 7.47±6 with 30% improvement and in group C it regressed from 6.48±4.47 to 4.09±2.76 with 37% improvement with p value <0.001 in all the groups.(Table 4)

Table 4: Mean MASI scores, percentage improvement, and P value of all the groups

Groups	Masi 0	Masi 12
Modified kligman group		
Mean ± sd	7.06 ± 6.5	4.3 ± 4.5
Percentage improvement		42%
P value <0.001		
Microneedling with TXA		
Mean ± sd	10.42 ± 8.3	7.47 ± 6
Percentage improvement		30%
P value		<0.001
Intralesional TXA		
Mean ± sd	6.48 ± 4.47	4.09 ± 2.76
Percentage improvement		37%
P value		<0.001



Graph 2: Percentage improvement in three groups.

The p value (t test) between 1^{st} and 2^{nd} group is 0.125 (p>0.05), and between 1^{st} and 3^{rd} group is 0.084 (p>0.05), indicating that there is no statistical significant difference between any two groups.

When compared in various types of melasma, Tranexamic acid showed marginally superior results in mixed and dermal melasma when compared to modified kligman formula.(Table 5)

Table 5: Results in various types of melasma

Type of melasma	Improvement of MASI in terms of percentage		
	Modified kligman	Microneedling + TXA	Intralesional TXA
Epidermal	43.22%	29%	37%
Dermal	32.99%	30.28%	35.58%
Mixed	35.48%	29.17%	37.43%

Clinical and dermoscopic photographs before and after treatment:

Group 1 : Modified kligman formula group

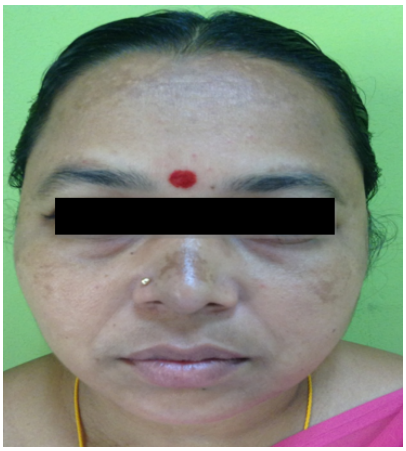


Fig. 1: Before treatment

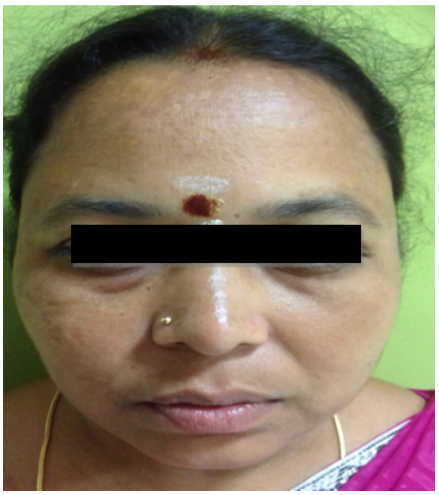


Fig. 2: After treatment

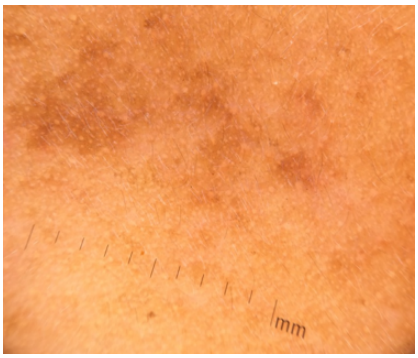


Fig. 3: Reticulate pattern of brownish pigmentation, with few specks of dark brown pigmentation.

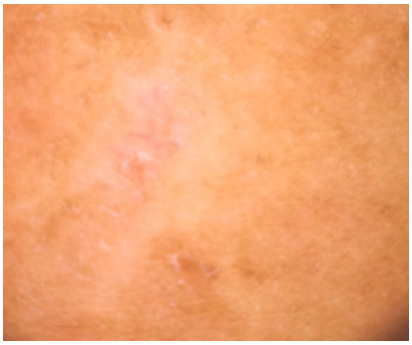


Fig. 4: Dissolution of pigmentation with perilesional hypopigmentation, telangiectasias are also seen over the treated lesional skin

Group 2: Microneedling with Tranexamic acid

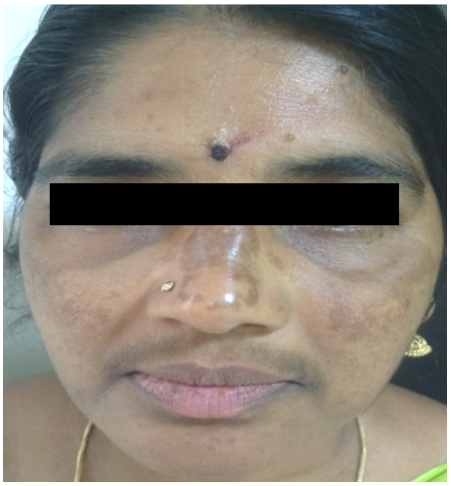


Fig. 5: Before Treatment

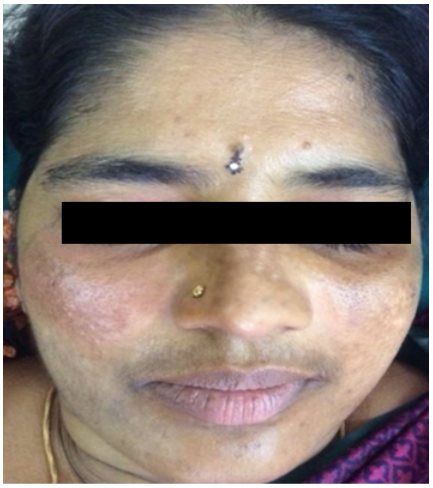


Fig. 6: After treatment

Fig. 7: Dark brown pigmented macules are seen diffusely

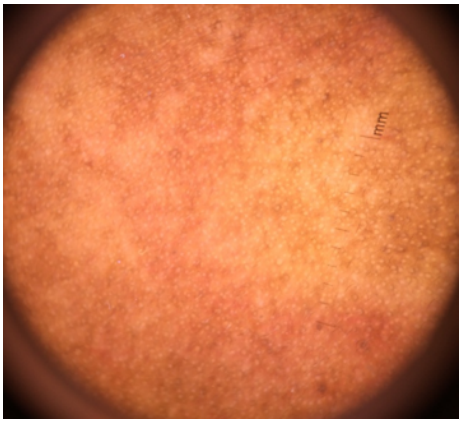


Fig. 8: Lightening of pigmentation and diffuse erythema over the treated areas.

Group 3: Intralesional Tranexamic acid

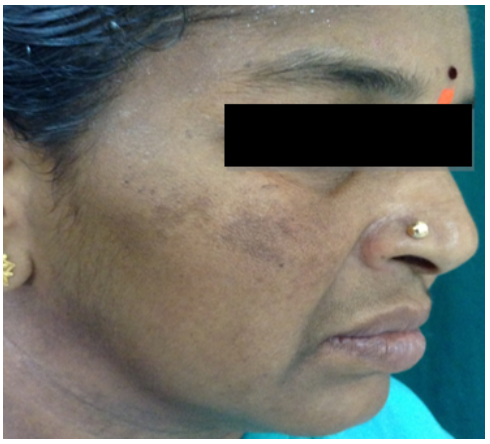


Fig. 9: Before treatment

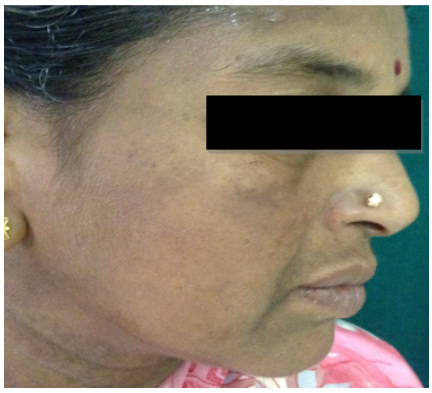


Fig. 10: After treatment

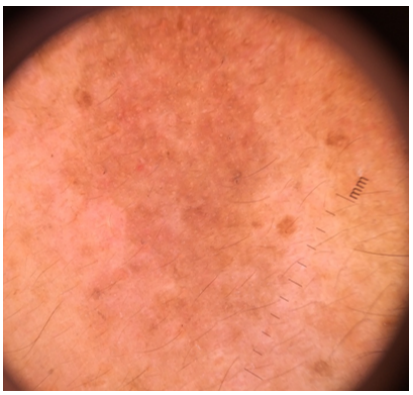


Fig. 11: Deep dark brown globules and specks of pigmentation indicating dermal melasma

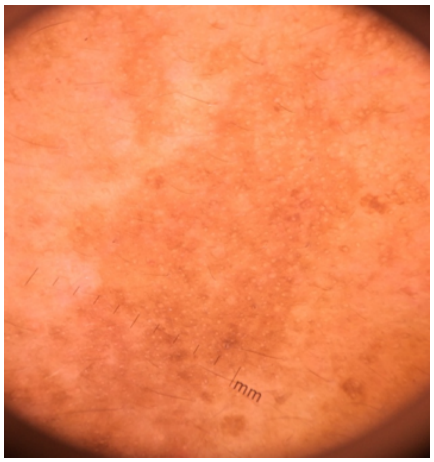


Fig. 12: Lightening of pigmentation and globules of pigmentation broke down into specks.

4. Discussion

Tranexamic acid is a hydrophilic drug that inhibits plasmin, clinically used as antifibrinolytic agent. The skin whitening effects of tranexamic acid was incidentally found when it was used in the treatment of aneurysmal subarachnoid hemorrhage. It is a synthetic derivative of lysine and its therapeutic role in melasma was first studied by Nijor as early as in 1979, but only limited data exist in the literature regarding its use in melasma. Recent studies have revealed that topical trans-4-(aminomethyl) cyclohexanecarboxylic acid (trans-AMCHA, TA), a plasmin inhibitor, prevents UV-induced pigmentation in guinea pigs and producing rapid skin lightening through its intradermal intralesional use.[12–14]

TA blocks the conversion of plasminogen (present in the epidermal basal cells) into plasmin by inhibiting plasminogen activator.[13,15] Plasmin activates the secretion of phospholipase A2 precursors, which act in the production of arachidonic acid (a precursor of melanogenic factors, such as prostaglandins and leukotrienes) and induce the release of basic fibroblast growth factor(bFGF) – a powerful melanocyte growth factor.[15] The plasminogen activator, which is generated by keratinocytes and has increased serum levels with oral contraceptive use and during pregnancy, increases the activity of melanocytes in vitro, and the blockage of this effect may be the paracrine mechanism by which TA decreases melasma hyperpigmentation.[15]

This study sought to address a new method of treatment using tranexamic acid in injectable solution.

A therapeutic trial was conducted to assess and compare the efficacies of topical Modified kligman′s formula (2%hydroquinone+0.025% tretinoin+0.1% mometasone), Microneedling with Tranexamic acid and Intralesional Tranexamic acid for a period of 3 months.

4.1. Modified kligman formula

In the modified kligman′s formula treated group, the response was excellent in 40%, good in 40%, fair in 20% with 42% reduction in MASI by the end of 12 weeks. The therapeutic benefits began to appear after 4 weeks of starting the therapy. Clinically, the areas of melasma were noted to become lighter with gradual decrease in size. Our results were in concordance with a study by Sarkar R et al[16] (2002), who had 33% and 63% reduction in MASI score at 12 and 21 weeks respectively. Two studies conducted by Torok HM et al[17] (2005), and Taylor SC et al[18] (2005), for a period of 12 months, showed 94% reduction in MASI score, which was higher than the present study(58%), as their study was conducted for a period of 12 months.

4.1.1. Microneedling +TXA

In the second group where microneedling was done followed by application of Tranexamic acid the response

was excellent in 7%, good in 7%, fair in 60% and poor in 26%, with 30% reduction in MASI by the end of 12 weeks. Clinically, homogenous patches of melasma reduced to specks of pigmentation. A study by Budamakuntla et al[19] (2013) showed 44.41% improvement which was higher than our study. When compared in various patterns of melasma, mixed and dermal melasma responded better with this method when compared to modified kligman formula.

When first and second groups were compared, P value is 0.125 (t test), which is not significant.

4.1.2. Intralesional TXA

In the Intralesional Tranexamic acid treated group, the response was excellent in 20%, good in 40%, fair in 26.6%, poor in 13.3% with 36% reduction in MASI by the end of 12 weeks. In an open study by Lee et al on 100 Korean women with melasma, tranexamic acid given intradermally (4 mg/ml) every week for 12 weeks caused significant decrease in MASI score (P value < 0.05), and 76.5% subjects reported lightening of melasma with minimal side effects.,[20] which was in favour to our study·

Overall, in the present study there was no significant difference statistically between the three modalities (p>0.05) with ANOVA t test.

Tranexamic acid showed marginally superior results in mixed and dermal melasma when compared to modified kligman formula. Which is explained by its mechanism of action, that it decreases number of blood vessels in lesional skin which is dermal related change in melasma.[21] It also inhibits α-MSH which is increased in lesional skin.

4.1.3. Post therapy advantages with Tranexamic acid:

1. There is a distinct advantage with Tranexamic acid where perilesional hallow which does not match with surrounding skin is not seen, which is generally seen with modified kligman formula.
2. Relapses which are commonly seen with modified kligman formula is less with Tranexamic acid.
   Dermoscopy played a major role for assessing treatment response.

5. Conflict of Interest

None.

6. Source of Funding

None.

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