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Efficacy Of Oral Tranexamic Acid In Combination With Modified Kligmans Regimen In Melasma Patients.

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ABSTRACT

This study was conducted to assess the efficacy of Oral Tranexamic acid as add on therapy with Modified Kligmans regimen in the treatment of Melasma. After randomization, drugs were administered to patients, for a period of 12 weeks. Group 1(control) received Modified Kligman's Regimen (0.01% Fluocinolone, 2% Hydroquinone, 0.05% tretinoin) topical once daily at bed time for 12 weeks. Group 2(study) received Oral Tranexamic acid 250mg twice daily 12 hours apart for 12 weeks along with Modified Kligman's Regimen After the treatment period of 12 weeks, the drugs were stopped and the patients were followed up for a further 12 weeks. MSI score was assessed at the baseline, 4 weeks, 8 weeks and at the end of 12 weeks. MSI scores consistently decreased both in the control and oral Tranexamic acid group. There was notable improvement in both the control and study groups and comparison between the intergroup shown statistically significant differences at the end of 12 weeks. In our study 50% reduction in MSI score from the baseline was obtained at the end of 8 weeks in the Oral Tranexamic group where as in the control group 50% reduction of MSI scores was obtained at the end of 12 weeks. Overall, at the end of 12 weeks study, the improvement seen was 80.72% in the Oral Tranexamic acid group and 64 % in the control group. This study shows that Oral Tranexamic acid in the dose of 250mg bd for 12 weeks is efficacious in the management of Melasma as an add on therapy to the standard treatment During the post treatment period, 6 (17.1%) patients from the control group and 2(5.7%) patients from the Oral Tranexamic acid group reported with a relapse of their condition. Hence recurrence rate was also lower in the Oral Tranexmic acid group. Based on this study finding it may be concluded that Oral Tranexamic acid used along with Modified Kligmans Regimen is found efficacious in the management of Melasma.

Keywords: Melasma, Modified Kligmans Regimen, Tranexamic acid, MSI score.

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INTRODUCTION

Melasma is a hyperpigmentary disorder which commonly affects face having symmetric pattern of distribution [1]. The word Melasma is derived from the Greek word "Melas" which means black represents the dark pigmentation of Melasma [2]. Melasma is one of the most common pigmentary disorders in dermatology clinics [3]. It is diagnosed clinically with the classical presentation of dark brown blotchy patches with irregular margins [4]. It occurs mostly in the sun-exposed areas of the face and less commonly involves other areas like arms, neck, nape of the neck. Clinical pattern can be malar, mandibular and Centro -facial.

It affects both the genders. Females are more commonly affected than males in the ratio of 9:1 [5]. It affects globally and the exact prevalence is unknown. The prevalence varies from region to region. Amount of UV radiation received and ethnicity of the population prevailing in the area decides the prevalence of melasma in that particular area. In India, the prevalence rate ranges from 20-30%. The most common age group affected is between 24-50 years [6].

Exact etiology of this disorder is unknown. The cause is multifactorial and it includes excessive sun exposure, genetic influence, hormonal imbalance and various medications like anti-seizure drugs, contraceptives, tricyclic antidepressants, tetracyclines, sulfonylureas etc [7]. Skin type also decides the preponderance of melasma. It is more prevalent in Asians and Hispanics especially of Fitzpatrick Skin type of III- VI. Indian skin type classified in the category of IV-VI and it is also one of contributing factor for the development of the disorders [8]. Pregnancy is also a causative factor, because 20% of the pregnant women develops melasma during pregnancy and hardly regresses after pregnancy [9, 10].

Among the factors mentioned above, excessive sun exposure is the most common cause [11]. Protection with sunscreen and clothing leads to clinical improvement of the lesion, thereby suggesting a strong correlation to excessive exposure to sun. UV radiations are of two types, of which UV-A radiations are responsible for photo damage and skin hyperpigmentation. UV radiation stimulates melanogenesis in the deeper layers of skin, leading to increased proliferation of melanocytes. This pigmentation is more pronounced in the face because of the increased distribution of melanocytes in that area [12].

Apart from causing cosmetic problems, it also causes a significant negative impact on the patient's quality of life with respect to social and psychological wellbeing [13, 14].

Even though a wide variety of drugs are available to treat this condition, effective treatment still remains a challenge to the treating physicians.

Modified Kligmans Regimen, popularly known as Triple combination therapy is the standard treatment used to treat Melasma. This regimen is a combination of (Flucinolone 0.01%, Hydroquinone 2%, tretinoin-0.05%). It is considered to be safe and widely used in the last few years. The major drawback in this regimen is the presence of steroids which can lead to telangiectasia and atrophic changes to skin on long term use. Hence, Tranexamic acid was selected for this study to preclude the adverse effects of steroids and to reduce the duration of treatment.

Tranexamic acid is an anti-fibrinolytic drug which is extensively used to treat menorrhagia and also in some surgical conditions to arrest bleeding. It acts by inhibiting tissue plasminogen activator. Keratinocytes are epidermal basal cells which contain plasminogen. They are involved in the regulation of proliferation and migration of melanocytes. Thus, these keratinocytes have a significant role in controlling melanogenesis. Tranexamic acid also acts on the plasminogen of keratinocytes and interfere with the production of melanin, thereby reducing the hyperpigmentation of melasma. Tranexamic acid has been tried in various forms such as topical, intralesional injections and oral tablet to treat this disorder with promising results. Oral Tranexamic acid has been found to have skin lightening effect by the above said mechanisms.

Hence, by knowing the skin lightening effect of Tranexamic acid, this open label, prospective, randomized controlled study was done to investigate whether oral administration of Tranexamic acid as add on to standard therapy (Modified Kligman's regimen) is effective in the treatment of Melasma.

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Aim And Objectives

Aim

- To study the efficacy of Oral Tranexamic acid as add on therapy with Modified Kligmans regimen in the treatment of Melasma.

Objectives

- To determine the improvement of symptoms with pigmentary changes and reduction in the size of Melasmic lesion based on the MSI score.
- To study the recurrences during the follow up period.

MATERIALS AND METHODS

Study Design

Randomized, open label, prospective, interventional, comparative study.

Study Center

Outpatient department of Dermatology, Tertiary care hospital, Chennai.

Study Period

One year

Study Duration

Treatment period of 12 weeks.

Post treatment follow up period of 12 weeks per patient.

Sample Size

70 patients (control group-35, Study group-35).

Inclusion criteria

- Patient females aged between 20 – 60 yrs.
- Patients newly diagnosed with Melasma.
- Patients willing to participate in the study.

Exclusion criteria

- Patients with comorbid illness like Diabetes mellitus, Hypertension, Thyroid disease and Renal Impairment.
- H/o Thrombotic events, Stroke, Myocardial Infarction.
- Pregnant women, lactating mothers, menstrual irregularities.
- Patients taking oral contraceptives, using cosmetics (turmeric, any form of lotion & facial creams).
- Patients with sensitive skin (burning sensation, allergy to any topical creams).
- Patients exposed to excessive sunlight (continous exposure).
- Photosensitivity disorders (SLE, porphyria,drugs).
- Underwent any recent surgeries (3 months) and undergoing cosmetic procedure.
- Immunocompromised individuals.
- Patients not willing to participate in study.

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Study Methodology

The study was conducted after obtaining approval from Institutional Ethics Committee and it was done in accordance with Good Clinical Practice (GCP) guidelines

After randomization drugs were administered to patients, based on the respective group they belonged to for a period of 12 weeks as mentioned below.

Group 1(control)	Group 2(study)
Standard Treatment	Standard Treatment along with Oral Tranexamic acid
n = 35	n = 35
Modified Kligman's Regimen (0.01% Fluocinolone, 2% Hydroquinone, 0.05% tretinoin) topical once daily at bed time for 12 weeks.	Oral Tranexamic acid 250mg twice daily 12 hours apart for 12 weeks along with Modified Kligman's Regimen.

After the treatment period of 12 weeks, the drugs were stopped and the patients were followed up for a further 12 weeks. Hence the total study period was 6 months for each patient.

Assessment of Participants

Clinical assessment comprising of detailed relevant history, general examination, vital signs and systemic examination were performed on every patient who were participating in the study.

Assessment Parameters

Both, Melasma lesions at the baseline and treatment outcome were assessed using Melasma Severity Index. (MSI)

Statistical Analysis

Statistical analysis was done using SPSS software, version. Mean and standard deviation values of MSI scale scores for different weeks were calculated. Intragroup analysis of MSI scores were performed using t-test for Equality of Means. A repeated measure of ANOVA was employed to assess the significance of changes in parameters between the two groups

RESULTS

Out of the 84 subjects who were screened, 70 patients satisfied the inclusion criteria. These patients were randomized and equally distributed between the control group (n=35) and study group (n=35). All the enrolled patients completed the study

Table 1

MSI SCORE					
DURATION	**CONTROL GROUP**		**STUDY GROUP**		**P VALUE**
	MEAN	**SD**	**MEAN**	**SD**	
0 WEEKS	**9.48**	**6.18**	**10.53**	**9.81**	**0.3**
4 WEEKS	**8.3**	**5.57**	**8.22**	**7.76**	**0.48**
8 WEEKS	**5.55**	**3.79**	**4.2**	**4.9**	**0.1**
12 WEEKS	**3.31**	**2.8**	**2.03**	**2.59**	**0.02**
P VALUE	**<0.01**		**<0.01**		

Table 1 shows MSI score of control and study groups from baseline to 12weeks. Intra group analysis showed a significant decrease in mean MSI score in both control group and study group from baseline to 12weeks. Between the groups MSI score is similar in both control and study groups from baseline to 8weeks. At 12weeks statistically significant improvement is seen in study group when compared to control group.

Adverse Drug Reactions

Out of 70 patients recruited in the study 13 patients reported adverse effects due to the medications. Most of the adverse effects were reported spontaneously. Most of the patients complained erythema after topical application of modified kligmans regimen. The most common side effect noted in Tranexamic acid group was hypopigmentation. A few reported hypomenorrhoea, nausea and abdominal pain after the intake of drug. The other participants tolerated the drug well. No life threatening or serious adverse drug reactions to drug occurred.

DISCUSSION

Melasma is one of the common hyperpigmentary skin disorder in our country. Tranexamic acid which acts by virtue of inhibition of melanosomes, thereby leading to depigmentation. Melasma is a disorder of excessive melanogenesis and UV light is the most important triggering factor for Melasma. Tranexamic acid being a lysine analogue specifically blocks the UV induced melanogenesis, thus providing benefit for the patients.

Study demographic profile showed no significant difference in the mean age in both the control and study groups. The average age in both the groups was 34. The number of patches and the duration of disease were also comparable in both the control and study groups. The pattern of distribution of melasma follows the Malar pattern which was the predominant finding in our study. This fact is in contrast to the study done by Quillen et al where the centro facial pattern predominates. This shows that the clinical presentation varies in different ethnic groups of population [15].

Among the women who were recruited, around 16 (21%) patients gave history of OCP's intake for a period of 6 months to 1 year following which they had developed melasmic lesions. This is in correlation with the previous studies conducted by Muzafer et al [16].

Among our patients 28% (19) gave family history of first-degree relatives had affected with Melasma. This finding is compatible with the study done by Sardesai et al which proves that 30% of patients with melasma had positive family history mentioned.

In our study MSI score was assessed at the baseline, 4 weeks, 8 weeks and at the end of 12 weeks. MSI scores consistently decreased both in the control and oral Tranexamic acid group. There was notable improvement in both the control and study groups and comparison between the intergroup shown statistically significant differences at the end of 12 weeks.

The mean MSI score of control was 8.3$\pm$5.57 and mean MSI score of study group was 8.2 $\pm$7.76. Comparison between the two groups shown no significant difference in the mean MSI scores at the end of 4 weeks and the 'P' value was 0.48.

At the end of 8 weeks the mean MSI score of control group was 5.5$\pm$3.79 and the mean MSI score of the test group was 4.2$\pm$4.9. The results of this intergroup analysis revealed a 'P' value of 0.1 which was statistically not significant. Whereas, the intragroup analysis revealed a significant fall in the MSI scores in both the groups.

MSI scores from the baseline to the end of 12 weeks where the mean of control group was 3.31$\pm$2.8 and the mean MSI score of the oral Tranexamic acid group was 2.03+2.59. Results of inter group analysis showed that there was statistically significant difference between the two groups with the 'P' value of 0.02.

In our study 50% reduction in MSI score from the baseline was obtained at the end of 8 weeks in the Oral Tranexamic group where as in the control group 50% reduction of MSI scores was obtained at the end of 12 weeks.

Overall, at the end of 12 weeks study the improvement seen was 80.72% in the Oral Tranexamic acid group and 64 % in the control group. This study shows that Oral Tranexamic acid in the dose of 250mg bd for 12 weeks is efficacious in the management of Melasma as an add on therapy to the standard

treatment. Our study results are compatible with the study done by Padhi T et al which showed 88% reduction of MSI score in tranexamic acid group [17].

During the post treatment period, 6 (17.1%) patients from the control group and 2(5.7%) patients from the Oral Tranexamic acid group reported with a relapse of their condition. Hence it was studied that recurrence rate was lower in the Oral Tranexmic acid group and this finding was consistent with the study done by Padhi T. et al.

Burning of skin was the common adverse event reported by patients in both the groups which were reported by Maji I et al for Modified Kligmans regimen were also commonly noted in our study. Patients were advised not to get exposed to direct sunlight and to use protective clothing over the face. Hypopigmentation was the common adverse event occurred in the Oral Tranexamic acid which was also reported by Aamir et al [18]. Calapai G et al in his study mentioned nausea and diarrhea as the common side effects were not occurred significantly in our study. No serious adverse events were reported in our study.

Limitations of the study

This study was done in a 12 weeks treatment period which is an insufficient time to study the course, treatment response and recurrence rates of chronic disease. This is an open label study and no blinding was done. The assessment parameters were subjective and more likely for observer bias. Hence these factors may be considered as the limitations of the study.

CONCLUSION

Based on this study finding it may be concluded that Oral Tranexamic acid used along with Modified Kligmans Regimen is found efficacious in the management of Melasma. It showed faster and sustained improvement in patients thus reducing the duration of treatment. It is being well tolerated and not associated with any serious side effects. So Oral Tranexamic acid in combination with the standard treatment can be considered rationale treatment option for treating Melasma and studies of longer duration are needed to confirm this finding.

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