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Original Research Article

Efficacy of oral tranexamic acid versus triple combination for the treatment of melasma: A prospective, double blinded randomised controlled trial

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ABSTRACT

Background: Melasma is a common acquired hypermelanosis characterized by irregular light to dark brown macules and patches seen mainly in women and over sun-exposed skin on the face. We have undertaken this RCT to compare the efficacy between oral Tranexamic acid and Topical Triple combination as Tranexamic acid is having good safety profile.

Objectives: To compare the therapeutic efficacy of oral Tranexamic acid versus Topical Triple combination for the treatment of Melasma using MASI score. To compare the adverse effects profile of each treatment modality.

Materials and Methods: Total subjects (66 patients) were divided into 2 groups (A and B, each with 33 patients) by simple randomization method.Patients and analysers were blinded to treatments. Group-A received topical triple combination cream once daily (15-minutes) at night for 8 weeks followed by maintenance regimen of biweekly application of product for 4 weeks and oral placebo tablets (calcium gluconate 250mg) twice daily for 12 weeks. Group-B received oral Tranexamic acid tablets 250mg twice daily for 12 weeks with topical placebo cream (Moisturizer) once daily at night for 8 weeks followed by maintenance regimen of biweekly application of product for 4 weeks. MASI score was assessed at baseline and monthly follow-up visits along with simultaneous serial digital photographs, with the recording of side effects.

Results: Both groups showed significant decrease in MASI score in each followup visits without any statistically significant difference.

Conclusion: In epidermal melasma topical triple combination is preferred over oral tranexamic acid. In dermal and mixed variety oral tranexamic acid is better.

1. Introduction

A blemish free skin is the desire of all human beings. Facial hyperpigmentation disorders usually occur due to an increased amount of melanin production and occasionally from an increase in the density of melanocytes.[1] It is usually a reflection of an increased amount of melanin either within the epidermis, the dermis, or both (mixed pattern). Melasma is a common, aquired, symmetric hypermelanosis, characterised by irregular light to dark brown macules and patches commonly involving the cheeks, forehead, upper lip, nose, and chin.[1] The melanocytes seem to undergo a functional alteration brought about by a combination of multiple factors, including persistent sun exposures, hormonal factors, and genetic predisposition.[2] Melasma can have a significant psychological impact on the patient and henceforth on Health-Related Quality Of Life (HRQoL).[3]The disease course of melasma follows the pattern of worsening hyperpigmentation during summer months and spontaneous improvement during

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winter months.[4] Three patterns of melasma are recognised clinically: centrofacial, malar and mandibular pattern based on the site of face involved. Three types of melasma are described on the basis of wood's lamp examination: an epidermal, dermal and mixed type.

Treatment of melasma involves the use of sunscreens (photoprotection) with topical hypo-pigmenting agents. Procedural therapies have been used to treat melasma with varying degrees of success.[5] First proposed in 1975, Kligman's formula has been the most widely used combination therapy for melasma worldwide. Hydroquinone is a hydroxy-phenolic chemical that inhibits tyrosinase, leading to decreased production of melanin. Various modifications to the original formula have subsequently been studied.[5] The US Food and Drug Administration approved modified Kligman's formula for the topical treatment of melasma, is a stable combination of fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05%. Furthermore it is the only US-FDA approved product containing hydroquinone.[6]

Till date none of its existing treatment modalities have provided quick and sustained result. One of the newer formulations that are being tried is tranexamic acid. "NijoSadako" in 1979 had used tranexamic acid to treat chronic urticaria. There was an accidental observation that within 2-3weeks of therapy that particular patient showed significant improvement in melasma. Then, he put on the first trial of tranexamic acid on melasma patients and showed that 1.5gm of daily dose of oral tranexamic acid is effective in the management of melisma.[7] Most of the effect was observed within 4 weeks of therapy. First publication in 1979 revealed that tranexamic acid has a role in the management of melasma. Tranexamic acid is a plasmin inhibitor used to prevent abnormal fibrinolysis to reduce blood loss. It is a synthetic derivative of the amino acid lysine and acts by reversibly blocking lysine binding sites on plasminogen molecules, thus inhibiting plasminogen activator from converting plasminogen to plasmin.[8,9] As plasminogen also exists in human epidermal basal cells and cultured human keratinocytes are known to produce plasminogen activator, there is basic rationale that tranexamic acid will affect keratinocyte function and interaction.

It is suggested that tranexamic acid inhibits UV induced plasmin activity in keratinocytes by preventing the binding of plasminogen to keratinocyte, which results in a less free arachidonic acid and diminished ability to produce prostaglandins and subsequently reduces melanogenesis in melanocytes. Furthermore it is suggested that tranexamic acid can inhibit the tyrosinase inducing activity of human melanocytes without affecting the viability of melanocytes. Hence, tranexamic acid can only stop the keratinocyte – activate - melanocyte pathway. It is the only modality that can actually prevent the activation of melanocyte by inhibiting the plasminogen activation system.[7] The advantage with tranexamic acid is its good safety profile and stability. It has been found that oral tranexamic acid is a safe and effective treatment in the management of melasma.[10] More studies are needed to evaluate its anti melasma potential. All the pre-existing treatment modalities of melasma aim at reduction of the formation of melanin from melanocyte (topical agents) and elimination of pre-existing melanin pigment (peeling, LASER). However these agents inevitably may activate melanocytes by different mechanisms like irritation, inflammation or by injuries to keratinocytes that lead to recurrent melasma or post inflammatory hyperpigmentation[11] and hence the need to develop alternative treatment options. Very few clinical trials have been conducted regarding the efficacy of oral tranexamic acid for the treatment of melasma in Indian scenario. So we have undertaken this Randomized Controlled Trial to compare the therapeutic efficacy between oral Tranexamic acid and topical triple combination as Tranexamic acid is having good safety profile.

The primary objective of this randomized clinical trial was to compare the therapeutic efficacy of oral tranexamic acid with topical triple combination for the treatment of melasma using MASI score with supportive digital photography. The secondary objective was to compare the adverse effects profile of each treatment modality.

2. Materials and Methods

It is a prospective, double blinded, randomized controlled trial done during one and half years study period from January 2016 to June 2017. Sample size was calculated considering the prevalence of melasma and it came around minimum of 27 patients in each study group (we have included 33 patients in each group}. Inclusion criteria was all patients with melasma who attended dermatology OPD, BIMS-Belagavi and were ready to participate in the 12 weeks study period. We have excluded patients on hormonal therapy, pregnant and lactating mothers, those with history of co-existing endocrinopathies, known allergy to tranexamic acid or sunscreen preparations, previous topical treatment for melasma within 2 weeks, oral tranexamic acid therapy within last 3 months and retinoic acid derivatives within one year prior to the initiation of the study, history of thrombosis, altered blood coagulation profile, altered blood urea and serum creatinine value. Patients with known and/or past history suggestive of APD, venous thrombosis were also excluded. All patients with melasma who came to dermatology OPD were screened and clinically evaluated and those eligible and willing for participation were investigated. They were subjected to routine investigations like Complete blood count, Differential leucocyte count, Platelet count, Bleeding time, Clotting time, Erythrocyte Sedimentation

Table 1: Showing age wise distribution of study subjects

		Group			
		A Group		B Group	
		Count	%	Count	%
Age	<30 years	7	21.2%	7	21.2%
	31 to 40 years	15	45.5%	14	42.4%
	41 to 50 years	10	30.3%	10	30.3%
	>50 years	1	3.0%	2	6.1%
	Mean ± SD	37.3 ± 8.3		38.3 ± 9.6	

Table 2: Distribution of histological types of melasma among study population.

		Group			
		A Group		B Group	
		Count	%	Count	%
Histological types of melasma based on Woods Lamp Examination.	Dermal	14	42.4%	18	54.5%
	Epidermal	16	48.5%	10	30.3%
	Mixed	3	9.1%	5	15.2%

Table 3: MASI score comparison between two groups at different visitsirrespective of type of melisma

	Group								P value b/w 2 groups
	A Group				B Group				
	Mean	SD	Median	P value	Mean	SD	Median	P value	
1st Visit	8.2	5.8	7.20		12.2	8.0	9.00		0.043*
1st Followup	6.5	5.2	6.00	0.001*	9.0	6.4	7.20	<0.001*	0.101
2nd Followup	5.0	4.6	3.90	<0.001*	6.8	6.1	4.80	<0.001*	0.409
3rd Followup	3.6	2.9	2.70	<0.001*	5.3	5.2	3.75	<0.001*	0.462

Table 4: MASI score comparison between two groups at different visits in subjects with epidermal type.

	Group						P value
	A Group			B Group			
	N	Mean	SD	N	Mean	SD	
1st Visit	16	8.6	4.5	10	9.8	5.4	0.545
1st Followup	15	5.6	3.4	9	8.0	4.6	0.150
2nd Followup	15	4.1	2.9	9	6.8	4.6	0.093
3rd Followup	14	2.4	1.1	8	5.3	4.4	0.026*

Table 5: MASI score comparison between two groups at different visits in subjects with dermal type of melasma

	Group						P value
	A Group			B Group			
	N	Mean	SD	N	Mean	SD	
1st Visit	14	6.1	5.2	18	9.9	6.4	0.082
1st Followup	11	6.0	5.2	14	6.4	4.6	0.844
2nd Followup	8	4.2	2.2	8	4.2	3.2	0.980
3rd Followup	7	4.3	2.4	7	3.6	2.8	0.561

Table 6: MASI score comparison between two groups at different visits in subjects with dermal type of melasma

	Group						P value
	A Group			B Group			
	N	Mean	SD	N	Mean	SD	
1st Visit	3	16.0	9.6	5	25.3	4.5	0.105
1st Followup	2	16.2	10.2	5	18.2	5.6	0.745
2nd Followup	2	14.4	12.7	5	13.5	9.8	0.919
3rd Followup	2	9.5	5.8	5	9.5	9.1	0.995

Table 7: Showing side effects profile observed in the study.

		Group			
		A Group		B Group	
		Count	%	Count	%
Side effects	Nil	26	73.1%	31	93.20%
	Erythema	7	26.9%	0	0.0%
	Gastritis	0	0%	2	6.80%

Rate, Random blood sugar, Renal and Liver function test, Fasting Lipid Profile, urine routine & microscopy. Blood Pressure recording of each patient was followed by ophthalmologic evaluation, woods lamp examination of melasma and assessment of Fitzpatrick's skin type with the help of skin tone analyser. Randomization was done by dividing the study group into A and B groups by simple randomization method with an intention of inclusion of minimum of 27 patients in each group (we have included 33 patients in each group). Each group contains both dermal and epidermal types of melasma. Patients, care providers and evaluators were blinded to treatment. MASI score and standard digital photography were recorded and then prescribed therapy was given for 12 weeks after taking written consent. Group A patients were given topical triple combination cream(modified Kligman's formula) once daily for short contact at night for 8 weeks followed by maintenance regimen of biweekly application of the product for another 4 weeks and oral placebo tablets (calcium gluconate 250mg) twice daily for 12 weeks. Group B patients were given oral tranexamic acid tablets 250mg twice daily for 12 weeks with topical placebo cream (moisturizer) once daily for short contact at night for 8 weeks followed by maintenance regimen of biweekly application of the product for another 4 weeks. MASI Score was assessed at every monthly follow up visits along with simultaneous serial digital photographs and recording of side effects if any. Both groups were advised on sun avoidance measures and strict usage of sunscreen with SPF30 throughout the study period. Patients were instructed to inform before using any other therapies during the treatment period. Clinical assessment of the patients were performed using MASI Score and standard digital photographs with simulataneous recording of side effects if any, at initial visit and at each follow-up visits at 4, 8, and 12th weeks, by same evaluator. Total MASI score = {(H+D) Arf X 0.15 + (H+D) Alf X 0.15 }+ {(H+D) Arm X 0.3 + (H+D) Alm X 0.3}+ {(H+D) Arc X 0.05 + (H+D) Alc X 0.05} {where rf =Right Frontal, lf =Left Frontal, rm = Right Malar, lm =Left Malar, rc =Right Chin, lc =Left Chin}. Total MASI score ranges from 0 to 48.

2.1. Statistical analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Chi-square test or Fischer's exact test (for 2x2 tables only) was used as test of significance for qualitative data. Yates correction was applied wherever chi-square rules were not fulfilled (for 2x2 tables only). MS Excel and MS word was used to obtain various types of graphs such as bar diagram, Pie diagram and Scatter plots. Continuous data was represented as mean and SD. Independent t test or Mann Whitney U test was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively.

3. Results

A total of 66 patients with melasma {9 (13.5%) males and 57 (86.5%)females} who fulfilled study criteria were included in the study with thirty-three (33) patients in each group A & B. The final results were analysed for 56 patients {29 patients in a group and 27 patients in B group} with lost to follow up of 10 patients {6 patients in A group and 4 patients in B group}. The age group of patients ranged from 18 to 60 years. Mean age of subjects in Group A was 37.3 ± 8.3 years and in Group B was 38.3 ± 9.6 years. There was no significant difference in mean age between two groups (p = 0.947) (Table 1). In Group A 51.5% had Fitzpatrick skin type 4 and 48.5% had FP skin type 5 and in Group B, 27.3% had FP skin type 4 and 72.7% had Fitzpatrick skin type 5. Group B had higher number of Fitzpatrick's skin type 5. This difference in FP skin type between two groups was statistically significant (p = 0.044*). In Group A, 42.4% had dermal type, 48.5% had epidermal type and 9.1% had mixed type of melasma. In Group B, 54.5% had dermal type, 30.3% had epidermal and 15.2% had mixed type of melasma. There was no significant difference in histological type of melasma between two groups (p = 0.304) (Table 2).

In Group A, Mean MASI score at 1^{st} visit was 8.2 ± 5.8, in Group B, 12.2 ± 8. This difference in MASI score between two groups was statistically significant. At other follow up visits there was no significant difference in MASI between two groups. But with in Group A, there was significant decrease in mean MASI from first visit to 3^{rd} followup visit. Similarly within Group B, there was significant decrease in mean MASI at 1^{st},2^{nd} and 3^{rd} followup visit compared to baseline (Table 3). Objective response to treatment in group A as studied by fall in MASI score (from 8.2 to 3.6) after 12 weeks is 55.1% while in

group B (from 12.2 to 5.3) 56.6%. (Table 3).

In epidermal type of melasma there was no significant difference in base line MASI score between A & B groups, but at 3^{rd} followup visit there was greater decrease in the MASI score in A group when compared to B group and the difference was statistically significant (Table 4).

In dermal type of melasma there was statistically significant difference in MASI score between two groups at baseline (p=<0.05). Therapeutic response as seen by decrease in MASI score at 3^{rd} followup visit is quite high in group B, when compared to group A. So in dermal variety B group appears to be more effective (Table 5)

In mixed type of melasma there was greater decrease in MASI score from baseline to 3^{rd} followup visits in group B when comapared to group A eventhough the difference is not statistically significant (Table 6).

In Group A, 73.1% had no side effects, 26.9% had moderate to severe local erythema and, in Group B 94% of them had no side effects and 6% had Gastritis. This difference in side effects profile between two groups was statistically significant (p = 0.008*). Side effects were higher in Group A (Table 7).

4. Discussion

Melasma is a common acquired hypermelanosis characterized by irregular light to dark brown macules and patches seen mainly in women and occurs mainly in sun-exposed skin on the face. All the pre-existing treatment of melasma aim at reduction of the formation of melanin from melanocyte and elimination of pre-existing melanin pigment. However these agents inevitably may activate melanocytes by different mechanisms like irritation, inflammation or by injuries to keratinocytes that lead to recurrent melasma or post inflammatory hyperpigmentation. Systemic tranexamic acid is effective in melasma and is having good safety profile.

On Wood's lamp, epidermal melasma shows complete enhancement, dermal has no enhancement and few areas of enhancement is seen in mixed type.

Our study showed similar age group involvement like other studies. Increased incidence of melasma in the age group of 31 – 40 years and 41 – 50 years may be due to increased occupational exposure to sunlight combined with physiological hormonal changes in reproductive life. More common incidence in females may be due to hormonal factors such as female sex hormones, lower Fitzpatrck skin types, higher prevalence of thyroid disorders, hormonal changes of pregnancy and reproductive life, oral Contraceptives usage etc. In Group A, mean MASI score at 1stvisit was 8.2 ± 5.8, in Group B it was 12.2 ± 8 because of more number of higher Fitzpatrick skin types in group B when compared to group A. This difference in base line MASI score between two groups was statistically significant. In subsequent follow up visits both groups showed statistically significant reduction in MASI score at subsequent follow-up visits. In epidermal type of melasma there was no significant difference in baseline MASI score between A & B groups, but at 3rd follow-up visit there was greater decrease in the MASI score in a group when compared to B group even though it's not statistically significant. So in epidermal type it's a group which is more effective. Therapeutic response as seen by decrease in MASI score at 4th visit when compared to base line is quite significant in group B, when compared to group A. So in dermal variety B group appears to be more effective. In mixed variety B group is more effective than a group, eventhough statistically not significant. Higher efficacy of tranexamic acid in both dermal and mixed variety of melasma may be due to its different mechanism of action because it is having more effect on dermal vascularity in addition to protection offered against UV induced melasma. Low incidence of side effects observed in our study and other studies on melasma may be due to low dose of oral tranexamic acid (500 to 1000mg per day) used for depigmentation pupose unlike in hemostatic purpose (high dose).

In conclusion oral tranexamic acid can be considered as an alternative mode of treatment in the management of melasma. Being a non-irritant drug with low side effects profile it can be safely prescribed for patients with melasma. It can be considered as an add on therapy to many available anti melasma therapies. By this we can cut short the duration of topical or other therapies and their potential long term side effects and also we can achieve rapid onset result which is a common expectation in all patients.In epidermal melasma it's better to prefer topical triple combination over oral tranexamic acid. In dermal and mixed variety it's better to prefer oral tranexamic acid over triple combination. More number of studies with larger sample size and longer duration of followup with oral tranexamic acid is needed to confirm its efficacy in melasma when compared to gold standard kligman's regimen. In near future, a better understanding of the molecular processes involved in cutaneous pigmentation, newer novel drugs and probably a genetic approach will bring new efficient therapies for melasma.

Limitations of our studies are small sample size, short duration of treatment and lack of follow-up after 12 weeks which was essential to know the recurrence rate if any.

5. Source of Funding

No external funding was received to carry out this work.

6. Conflict of Interest

None.

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