

Research Article

Role of oral tranexamic acid in melasma

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Abstract:

Context: Melasma is a chronic, acquired hyperpigmentary disorder. Plethora of treatment options are available but none is promising and recurrence is common. Treatment of melasma using oral tranexamic acid is a novel concept.

Aims: To compare the efficacy of oral tranexamic acid with conventional topical therapy for the treatment of melasma.

Design: Prospective, parallel, randomized, comparative, clinical study.

Methods and Material: It was a prospective, randomized controlled trial conducted among 104 melasma patients. Patients were assigned into two groups (group A and group B) consisting of 52 patients each. Group A was given routine treatment measures along with oral Tranexamic Acid and photoprotection while Group B was treated only with routine topical measures and photoprotection. Oral Tranexamic Acid was prescribed at a dose of 250 mg BD for three months and patients were followed for three months. Clinical response was evaluated on the basis of Melasma Assessment Severity Index (MASI). Mean scores between the two groups were then compared.

Results: The MASI scores at baseline, 8 weeks and 12 weeks in group A were 18.24 + 1.05, 6.13 + 4.9 and 2.19 + 2.3 respectively and in group B were 15.42 + 1.09, 11.07 + 9.16 and 7.99 + 6.05. MASI score reduction percentage at the end of 12 weeks was 88% and 54.6% respectively indicating a greater decrease in the group taking Tranexamic acid and was statistically significant for both the groups with $P < 0.05$

Conclusion: Addition of oral tranexamic acid with the triple combination results in rapid and sustained response with less chances of relapse. So tranexamic acid is a great boon for the melasma patient as well as for the clinicians.

Key-words: Melasma, oral tranexamic acid, triple combination, sunscreen.

Key Messages: Plethora of therapeutic modalities, especially the gold standard hydroquinone have been used in the treatment of melasma. Inherent side effects, have limited efficacy and frequent relapses on discontinuation of therapy. This article focuses on newer and experimental agent, which could potentially be used as treatment for melasma. Oral tranexamic acid could offer a ray of hope in the future.

Introduction:

Melasma is a chronic, acquired hyperpigmentary disorder presenting over the sun-exposed skin. It is most commonly observed in women of reproductive age group and dark-skinned individuals [1] with Fitzpatrick skin types III-V [2], rarely in postmenopausal females and males (10% of cases). Causative factors for melasma are genetic susceptibility, pregnancy, sex hormones,

contraceptive pills, cosmetics, Ultraviolet (UV) light exposure and phototoxic drugs [3].

Despite the plethora of treatment modalities are available, like topical medications such as hydroquinone, azelaic acid, kojic acid, procedural treatments like chemical peels, microdermabrasion and LASER, like Q-switched Nd: YAG laser, intense pulse light. But still melasma poses a great challenge as its treatment

can be often unsatisfactory with high recurrence rates. Presently topical hydroquinone is considered to be the gold standard among topical treatments of melasma. [4]

The use of oral Tranexamic acid as a novel concept for treatment of melasma. Its use in the treatment of melasma was first reported in 1979 by Nijo in Japan [5]. Previously oral Tranexamic acid was used for chronic urticaria [6]. Studies have found Tranexamic acid, a traditional haemostatic drug, to also inhibit plasminogen-keratinocyte interaction decreasing the tyrosinase activity leading to decreased melanin synthesis from the melanocytes. [7,8] Thus explaining its effect on melasma lesions and also in preventing UV-induced pigmentation [9-13]. Very few studies have been conducted regarding the efficacy of Tranexamic acid in melasma. This study was conducted with the aim to compare the efficacy of oral tranexamic acid plus triple combination cream with triple combination cream alone in facial melasma. The objectives of the study were to observe the degree of improvement in pigmentation objectively using MASI score at baseline, 8 weeks and 12 weeks as well as the safety profile of Tranexamic acid in patients with Melasma.

Subjects and Methods:

This was a prospective, randomized, interventional, comparative, clinical study was conducted in 104 patients of melasma attending the skin OPD of the UPUMS, Saifai, Etawah from June 2018 to November 2019 after taking ethical clearance from the institutional review committee. The sample size was calculated at 104 taking prevalence of 10% in Indian population with confidence level at 95% and margin of error at 0.05.[14]

Inclusion criteria:

- Patients with facial melasma, of both sexes, any age group, willing to undergo treatment and to come for regular follow up

Exclusion criteria:

- Pregnant and lactating females
- History of thromboembolism (Active/Past)
- Coagulopathies (approved by laboratory test)
- Severe renal impairment
- Allergic to TXA
- Photosensitizing drugs
- Thyroid disorders

- Not willing for follow up
- Unrealistic expectation
- Melasma therapies within last 6 months
- Refused for photograph.

All patients were randomly allocated in 1:1 ratio with alternate randomization into groups A and B. Group A patients were advised to take Oral Tranexamic acid 250mg twice daily for three months along with topical triple combination at bed time. Group B patients were advised to use topical triple combination alone. All patients were advised to apply broad spectrum sunscreens with an SPF of 20.

All the patients were followed up for six months to look for any recurrence.

All the patients who fulfilled the inclusion criteria were included. General examination, detailed ophthalmological examination, with special emphasis on colour vision abnormalities and retinal artery occlusion, was done at each visit to rule out any side effects of tranexamic acid. Complete blood count, coagulation profile and liver function test were done in all patients before prescribing them tranexamic acid and also at each visit to rule out any coagulation abnormality.

Treatment evaluation was done by clinical examination, Melasma Area Severity Index (MASI) scoring, and colour photographs, scoring and colour photographs were taken at baseline, 8 weeks and 12 weeks after treatment.

MASI is a scoring system given by Kimbrough-Green CK et. al. used to quantify the severity of melasma.[15] The face was divided into four areas [forehead (F) 30%; right malar (MR) 30%; left malar (ML) 30%, chin (C) 10%] and each area was given a numerical value (A, 0-6). The sum of severity for darkness (D, 0-4) and homogeneity (H, 0-4) of melasma was multiplied by the numerical value and percentage of each area.

$MASI = 0.3(DF + HF) AF + 0.3(DMR + HMR) AMR + 0.3(DML + HML) AML + 0.1(DC + HC) AC$

The maximum and minimum score for MASI can be 48 – 0 respectively. SPSS ver 23 was used for the statistical analysis. Mean MASI scores were compared with students' T-test and statistical significance was compared. Variables were considered significant for a confidence interval of 95% ($P < 0.05$) Patient satisfaction score was subjectively graded on the basis of four-point Likert scale: excellent, good, fair, and poor. Possible side effects of Tranexamic acid were noted on follow up of patients.

Results:

There were 104 patients included in the study with 91 females and 13 males of age between 22years to 48 years with a mean age 33.7+2.6. (Table.1) Majority of the subjects in both the groups had Epidermal type of melasma with the most common distribution pattern being Centro-facial. (Table. 2)

Table 1. Age wise distribution of melasma patients

AGE (in years)	GROUP A (n = 52)	GROUP B (n = 52)	Total (n = 104)
Mean age (in years)	36 + 8.9	35.7 + 6.2	35.85 + 7.6
<25	02	01	03
25-34	19	19	38
35-44	25	23	48
>45	06	09	15

Table 2. Classification of Melasma

Type of melasma	Group A	Group B
Epidermal	34	30
Dermal	07	05
Mixed	11	17
Distribution of melasma		
Centro-facial	41	40
Malar	08	07
Mandibular	03	05

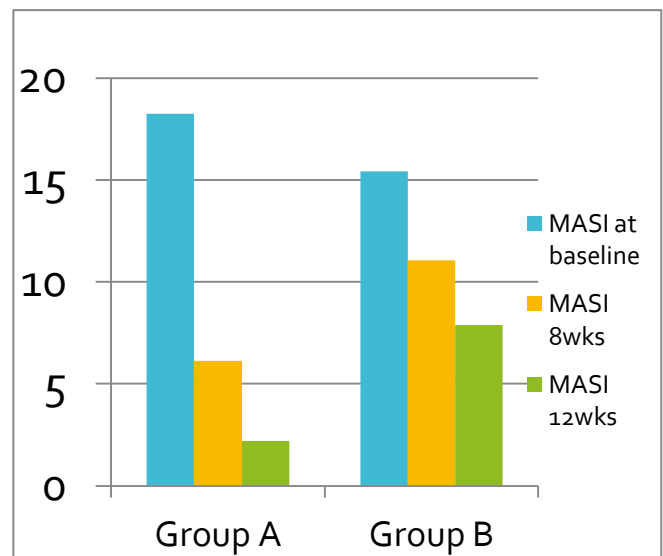
The MASI scores at baseline, 8 weeks and 12 weeks in group A were 18.24 + 1.05, 6.13 + 4.9 and 2.19 + 2.3 respectively and in group B were 15.42 + 1.09, 11.07 + 9.16 and 7.99 + 6.05. MASI score reduction percentage at the end of 12 weeks was 88% and 54.6% respectively indicating

a greater decrease in the group taking Tranexamic acid and was statistically significant for both the groups with P< 0.05 [Table 3] [Chart 1]

Table 3. Melasma area severity index-comparison at baseline, 8 weeks and 12 weeks.

	MASI at baseline	MASI at 8 weeks	MASI at 12 weeks	MASI reduction %	P value
Group A	18.24+1.05	6.13+4.9	2.19+2.3	88%	0.000
Group B	15.42+1.09	11.07+9.16	7.99+6.05	54.6%	0.006

Chart 1. Melasma area severity index-comparison at baseline, 8 weeks and 12 weeks.



Patient Satisfaction Assessment in group A revealed that majority of the patient felt improvement was excellent (45.4%) and only a few graded the response to be poor (6.9%) while majority of patients in group B found the improvement to be fair (40%) and more patients felt the response was poor (19.3%). [Table 4]

Table 4. Comparison of Patient Satisfaction Assessment between Group A and B

	Group A (n=52)	Group B (n=52)
Excellent	45.4%	8.5%
Good	36.9%	32.3%
Fair	10.8%	40%
Poor	6.9%	19.3%

Mild side effects were observed in few patients of both groups. No major systemic side effects were seen in any of the patients. [Table 5]

Table 5 Comparison of adverse effects among both groups

Adverse effects	Group A	Group B
Erythema	01	02
Abdominal cramps	02	-----
Hypomenorrhea	02	----
Hypopigmentation	02	01
Nausea	01	-----
Other systemic side-effects	-	-----



Figure 2: Pictures showing excellent response in a 24-year-old male patient of melasma after 12 weeks of therapy.



Figure 3: Before and after photographs of patient on Tranexamic acid for 12 weeks.



Fig1. 44 year old female with significant improvement seen after 12 weeks therapy with Tranexamic acid.

Discussion:

Melasma is an acquired, chronic, recurrent, symmetrical hyper melanosis typically occurring on the face (lower cheeks, forehead, nose and upper lip).[3]Melasma is more common in women, accounting for 90% of all cases, and appears in all racial types, particularly those with skin types III-V who live in areas of high ultraviolet (UV) radiation. The persistent nature and profound cosmetic disfigurement lead to significant stress and embarrassment for the patient.

Melasma has been an enigma as far as the treatment is concerned. The constant sun exposure as well as the poor response of dermal component to treatment have been considered major cause of resistance. The modalities used so far have their inherent side effects, have limited efficacy and often, the condition relapses on discontinuation of therapy. As there is no perfectly satisfactory agent for melasma, efforts are ongoing for finding newer, safer and an ideal treatment.

The addition of Tranexamic acid for the treatment of melasma is a novel concept. Its role in the

treatment of melasma was a serendipitous discovery with improvement of melasma in a patient who was being treated with Tranexamic acid for chronic urticaria by Nijo in 1979 [5]. Previously used as an antifibrinolytic agent, Tranexamic acid has been found to inhibit plasminogen-keratinocyte interaction decreasing the tyrosinase activity causing decreased melanin synthesis from the melanocytes.[7][8]

Very few clinical trials have been conducted regarding the efficacy of Tranexamic acid (oral, topical or intralesional) for the treatment of melasma.

After its discovery by Nijo [5], other Japanese researchers took interest in studying the role of Tranexamic acid in melasma. Sadako et al [16], Hajime et al [17], Higashi et al [18] and Zhu et al [19] in their studies used Tranexamic acid in doses ranging from 0.75-1.5g/day orally with or without vitamin C and found significant improvement in patients with melasma. In all these studies, GI upset was the only common side effect reported (around 5% patients) with no change in coagulation tests observed in any of the studies

Subsequently, researchers studied Tranexamic acid for treatment of melasma in lower doses (500mg/day). Cho et al (2011) [11] used 500mg/day as additional therapy with IPL or Nd:YAG laser and found significantly lower mMASI score in the Tranexamic acid group. Wu et al. (2012) used 250mg twice a day on 256 patients with significant improvement in pigmentation. [13].

In our study, patients receiving oral Tranexamic acid had 88% reduction in mean MASI score at the end of 12 weeks as compared to only 54% reduction in patients only on conventional therapy (18.24±1.05 vs 15.42±1.09 at baseline and 2.19±2.3 vs 7.99±6.05 at 12 weeks). In a previous study, Padhi and Pradhan [20] observed 54% reduction in mean MASI scores after 8 weeks of Tranexamic acid compared to 18% reduction in the control group. Similar observations were obtained in a study from Nepal by Karn et al [2]. Tan et al [21] treated patients with Tranexamic acid 250mg BD along with topical therapy for 6 months and found 69% reduction in mean MASI scores. Lee et al [22] did a retrospective analysis of patients treated with Tranexamic acid 250mg BD and found that 89.7% patients had improved.

Patient's satisfaction was also taken into consideration in our study. According to the

patients on Tranexamic acid - 45.4% rated improvement to be excellent, 36.9% good, 10.8% fair and only 6.9% poor. While among the patients on topical therapy alone, only 8.5% felt excellent improvement and 19.3% found response to be poor.

Tranexamic acid via other routes of administration have also been tried for melasma. Shetty VH & Shetty M [23] conducted a study using intradermal Tranexamic acid injections (4mg/ml) at 3-weekly intervals and found improvement in 61.3% patients with 35% reduction in mean MASI score. Similarly, Lee et al [9] gave weekly injections for 12 weeks with good results and no significant side effects. Topical Tranexamic acid is available in 2% emulsion, 3% cream, and 5% solution form. Studies by Konda et al [10] and Ebrahimi B & Naeini [24] have found topical tranexamic acid to be effective but not significantly superior to the conventional therapy. However, considering the potential long-term side effects of conventional triple therapy, topical tranexamic acid is relatively safe for use as maintenance therapy.

Regarding the safety profile, there were only a few minor side effects reported with no serious adverse effect in any of the groups. Hypomenorrhea was reported by 2 patients (3.8%) and Gastrointestinal discomfort by 3 patients (5.7%). Padhi & Pradhan [20] also reported hypomenorrhea (4.1%) and Gastrointestinal discomfort (5.4%) as the commonest side effects. 8.1% patients had reported hypomenorrhea in the study by Wu et al [13], which was reversible on stopping the treatment. Lee et al [22] reported that one patient had developed deep vein thrombosis but that turned out to be a case of familial protein S deficiency.

These studies have all led to the consensus that Tranexamic acid is effective in melasma in doses of 500-750mg/day, about 1/6th of the doses used for its hemostatic action. Therefore, making it a safer drug with a significantly lower risk of complications associated with the hemostatic dose.

Limitations of our study are that it was not a blinded study and the duration of the study was short limited to a single tertiary care center. Large scale multicenter randomized controlled studies with long term follow up are required. Therapy needs to be studied across all the ethnic groups. The duration of therapy needed to provide

maximum improvement along with least risk of recurrence needs to be established.

Conclusion

The addition of Tranexamic acid with the triple combination results in rapid and sustained response. Tranexamic acid is the only drug so far used in melasma capable of preventing activation of melanocyte by sunlight, hormones, and injured keratinocyte via inhibition of plasminogen-activator system. Not only does it reduce the formation of melasma, but also the chances of recurrence. The recommended dose based on all the recent studies would be 250mg two times daily and that longer duration of therapy would be more beneficial. The safety profile at this dose has been explored and prescribing it routinely requires following simple guidelines and to look out for contraindications. While further insight into the aetiology of melasma continues, Tranexamic acid offers a safe, effective and a promising therapy for treatment of melasma.

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