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Jacobs Journal of Experimental Dermatology and Research

Research Article

# Oral Tranexamic Acid Versus Triple Combination for The Treatment of Melasma

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*Received:* 09-15-2015

*Accepted:* 10-12-2015

*Published:* 10-16-2015



## Abstract

### Introduction

The treatment of melasma is very frustrating and despite newer emerging therapies of melasma, the melasma recurs again.

### Aim

To compare the efficacy of oral tranexamic acid versus triple combination for the treatment of melasma.

### Methods

A prospective study of fifty patients of melasma was conducted. The patients were divided into two groups of twenty five patients each. In group I, the patients were given oral tranexamic acid 250 mg twice daily for 16 weeks and in group II, triple combination with fluocinolone acetonide, hydroquinone and tretinoin was given for 16 weeks.

### Results

There was no statistically significant difference in reduction of MASI scores at the end of 16 weeks between the two groups ($P > 0.05$). Subjective response, as graded by the patient, showed good or very good response in 80% in group I(Supplementary Figure 1& Supplementary Figure 1a) and 70% in group II (Supplementary Figure 2& Supplementary Figure 2a). In group I (tranexamic acid group) , 64% reduction of MASI score was seen, in group II (triple combination group) 56% reduction of MASI score was seen.But the comparative efficacy in all the two groups was statistically insignificant. Relapse was seen in 3 cases after a follow up of 6 months in triple combination group and in none of the patients in tranexamic acid group.

### Conclusion

To conclude, for the treatment of recurrent melasma, oral tranexamic acid provides satisfactory treatment compared to other treatment modalities.

**Keywords**: Melasma; Tranexamic Acid; Melanin; Tyrosinase; Hyperpigmentation

## Introduction

Melasma is an irregular brown or grayish-brown facial hypermelanosis, often affecting women, especially those living in areas of intense ultraviolet radiation. The precise cause of melasma remains unknown; however, there are many possible contributing factors. The common contributing factors include genetic predisposition, pregnancy, use of oral contraceptives, endocrine dysfunction or hormone treatments and exposure to UV light [1,2].

Generally, melasma is classified into one of 3 histologic types: epidermal, dermal, and mixed. However, some also include a fourth type known as Wood's light in apparent. Under

Wood's light the epidermal type often shows a darkening of color when examined, as the light emitted by Wood's lamp is absorbed by the excess melanin. The dermal type, however, will not show this accentuation. The mixed type involves a deposition of melanin in both the epidermis and the dermis and color enhancement with Wood's light is seen is some places of the skin, but not others. There are 3 clinical patterns recognized on the basis of clinical examination. These include a centrofacial, malar, and mandibular pattern. The centrofacial is the most common pattern of melasma and involves the cheeks, forehead, upper lip, nose, and chin. The malar pattern has lesions limited to the cheeks and nose, and the mandibular pattern has lesions that occur over the ramus of the mandible [3,4].

Tranexamic acid (TA) is analogue of aminocaproic acid. Chemically, TA is identified as trans-4-cyclohexanecarboxylic acid and is shown to prevent UV- induced plasmin activity. Tranexamic acid helps in the inhibition of melanin synthesis by tyrosinase in melanocyte and the reactive oxygen species related proliferation of melanocyte [5,6]. TA acts by attaching itself to the lysine binding sites of plasmin and plasminogen, preventing ultraviolet rays induced pigmentation. Ultraviolet (UV) irradiation induces plasminogen activator synthesis and increases plasmin activity in keratinocytes, which stimulates the release of arachidonic acid. TA also inhibits melanin synthesis in melanocyte by interfering with the interaction of melanocytes and keratinocytes through inhibition of plasminogen/plasmin system. Tranexamic acid has been shown to prevent UV-induced plasmin activity which leads to a decrease in arachidonic acid and subsequently prostaglandins, thereby decreasing tyrosinase activity. Also, it reverses smelasma related dermal changes such as vessel number and increased numbers of mast cells. Moreover, tranexamic acid is used as a hemostatic and the hemostasis of TA is based on the antifibrinolytic effect and does not interfere with blood clotting parameters [7].

Absorption of tranexamic acid after oral administration in humans represents approximately 30% to 50% of ingested dose and bioavailability is not affected by food intake. Tranexamic acid is one of the modalities that can actually prevent the activation of melanocyte by sunlight, hormonal influence and injured keratinocyte through the inhibition of the plasminogen activation system. It can not only reduce the formation of melasma, but also reduce the likelihood of recurrence after other treatment modalities themselves activate melanocytes.

Various indications of tranexamic acid are melasma ,menorrhagia, epistaxis, haematuria and hereditary angioedema [8]. There are various contraindications of TA like severe renal failure, active intravascular clotting, thromboembolic disease, colour vision disorders and subarachnoid bleeding. The commonest side effects of tranexamic acid include gastrointestinal irritations such as nausea, diarrhoea and abdominal pain. Thromboembolism, pulmonary embolism and myocardial infarction have rarely been reported [9].

Triple combination has been used in melasma since long. It consists of combination of hydroquinone, retinoic acid and fluocinolone acetonide [10]. The main problem with triple combination is its irritation potential with long term use [11]. Another problem with triple combination is that melasma may clear after its use but recurrences are common after its discontinuation. Moreover, it is also available as over the counter drug at some places and so its misuse is very common leading to skin atrophy, persistent erythema and hypertrichosis of the face [12, 13].

## Aim

1. To study the efficacy of tranexamic acid for the treatment of melama.

2. To compare the efficacy of oral tranexamic acid versus triple combination for the treatment of melasma.

## Materials and Methods

A prospective study of fifty patients of melasma was conducted. The patients were divided into two groups of twenty five patients each. In group I, the patients were given oral tranexamic acid 250 mg twice daily for 16 weeks and in group II, triple combination with fluocinolone acetonide, hydroquinone and tretinoin was given for 16 weeks. Written informed consent of all the patients was taken before the start of the study and prior approval of hospital ethical committee was taken for the study. MASI score was done at the start of the treatment and then every four weeks. Digital photography was done at each visit. The patients were instructed to apply broad spectrum sunscreens during the day time. Follow up of the patients was done for 6 months after the completion of the treatment to see for any relapse of melasma. For subjective improvement before and at the completion of the study, the response in each patient was graded as: no response if there was no change in MASI score at the end of 12 weeks; mild response if there was less than 25% change; moderate response with 25 to <50% decrease in MASI; good response if there was 50 to <75% fall in MASI score; very good response with more than 75% fall in MASI score. Before the start of the study, Wood's lamp examination was done in all the patients to see the depth of melisma. Routine investigations of the patients were done including the haematological profile, liver function tests and kidney function tests. Specialized investigations included prothrombin time and activated partial thromboplastin time which were done before the start of the study and the every 2 months. The data was collected, tabulated and the results were analyzed statistically using chi square test.

## Inclusion Criteria

The following patients were included in our study:

1. Patients with epidermal and mixed melasma.

2. Patients with realistic expectations.

## Exclusion Criteria

The following patients were excluded from our study:

1. Pregnant and lactating females
2. Patients with history of thrombosis or abnormal bleeding profile
3. Patients with dermal melasma
4. Patients with thromboembolic disease
5. Patients with severe renal failure
6. Patients with unrealistic expectations

## Results

In our study, commonest age group (80%) patients were in the age group of 20- 40 years, 16% patients were between 41 – 60 years of age and 4% patients each were less than 20 years of age (Table 1). Females outnumbered males and females: males ratio was 5.2: 1(Table 2). 48% cases were of epidermal melasma and 52% patients had mixed melisma. Most of the patients (70%) had duration of melasma between 2- 5 years, 10% patients had duration of less than 2 years and 20% patients had duration of melasma more than 5 years. The most common pattern was malar (40%) followed by mixed in 30% patients, centrofacial pattern in 20% patients and10% patients had mandibular pattern (Table 3)

**Table 1 .**Table Showing Age Distribution of Patients.

| SR NO | AGE DISTRIBUTION | GP I | | GP II | |
|---|---|---|---|---|---|
| | | **NO** | **%** | **NO** | **%** |
| 1 | 20 > | 1 | 2% | 1 | 2% |
| 2 | 40 - 20 | 18 | 36% | 22 | 44% |
| 3 | 60 41- | 6 | 12% | 2 | 4% |

**Table 2.** Table Showing Sex Distribution of Patients.

| **SR NO** | **SEX DISTRIBUTION** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | FEMALES | | | | MALES | | | |
| 1 | GP I | | GP II | | GP I | | GP II | |
| 2 | NO | % | NO | % | NO | % | NO | % |
| 3 | 22 | 44% | 20 | 40% | 4 | 8% | 4 | 8% |

**Table 3.** Table Showing Pattern of Melasma.

| **SR NO** | **PATTERN** | **GP I** | | **GP II** | |
|---|---|---|---|---|---|
| | | NUMBER | % PERCENTAGE | NUMBER | % PERCENTAGE |
| 1 | MALAR | 8 | 16% | 12 | 24% |
| 2 | CENTROFACIAL | 5 | 10% | 5 | 10% |
| 3 | MANDIBULAR | 2 | 4% | 3 | % 8 |
| 4 | MIXED | 7 | 14% | 8 | % 14 |

**Table 4.** Table showing MASI score before and after treatment.

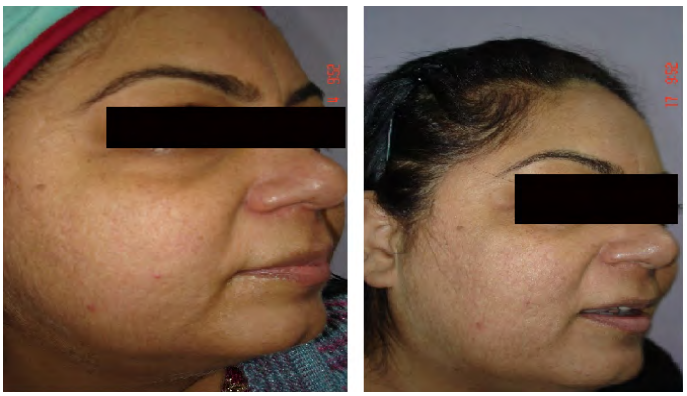
| SR NO | MASI SCORE | | | |
|---|---|---|---|---|
| | GROUP I | | GROUP II | |
| 1 | Before treatment | After treatment | Before treatment | After treatment |
| 2 | 25±3.25 | 6.34±9 | 2.68±24 | 4.69±10 |

**Table 5.** Table Showing Side Effects of Treatment.

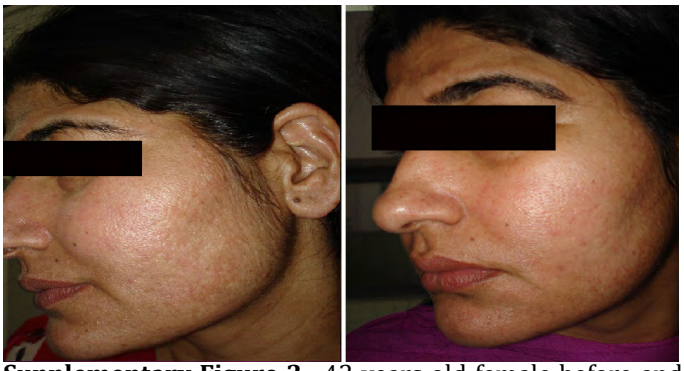
| **SR NO** | **SIDE EFFECT** | **GROUPS** | |
|---|---|---|---|
| | | GROUP I | GROUP II |
| 1 | Erythema | - | 9(36%) |
| 2 | Post inflammatory hyperpigmentation (PIH) | - | 6(24%) |
| 3 | Transient headache | 3(12%) | - |
| 4 | Gastrointestinal side effects | 3(12%) | - |
| 5 | Reccurrence of melasma | 3(12%) | 6(24%) |

## Discussion

In our study, was no statistically significant difference in reduction of MASI scores (Table 4) at the end of 16 weeks between the two groups ($P > 0.05$). Subjective response, as graded by the patient, showed good or very good response in 80% in group I (Supplementary Figure 1) and 70% in group II (Supplementary Figure 2). In group I (tranexamic acid group), 64% reduction of MASI score was seen, in group II (triple combination group) 56% reduction of MASI score was seen. But the comparative efficacy in the two groups was statistically insignificant. Relapse was seen in 3 cases after a follow up of 6 months in triple combination group and in none of the patients in tranexamic acid group. Regarding side effects of peels, erythema was seen in 30% patients in triple combination group and in none of the patients in tranexamic acid group,post inflammatory hyperpigmentation was seen in 20% patients in triple combination group and in none of the patients in tranexamic acid group. Other side effects including transient headache, gastrointestinal side effects were seen in 10% patients in tranexamic acid group (Table 5). Recurrence of melasma was seen in 20% patients in triple combination group and 10% patients in tranexamic acid group.



**Supplementary Figure 1.** 47 years old female before and after treatment with oral tranexamic acid.



**Supplementary Figure 2** . 42 years old female before and after treatment with triple combination.

Tranexamic acid is an oral agent that has been shown to prevent UV induced plasmin activity, which leads to a decrease in arachidonic acid and subsequently prostaglandins, thereby decreasing tyrosinase activity [14,15]. Free arachidonic acid stimulates melanogenesis via its metabolite, prostaglandin [16,17]. In other pathway, increased plasmin itself elevates a-melanocyte-stimulating hormone, which activates melanin synthesis in melanocyte. Moreover, TA is found to be similar to tyrosine in the part of its structure, which can competitively inhibit the activity of tyrosinase. In summary of previous reports, TA was considered to help prevention of pigmentation after UV irradiation. TA can prevent UV-induced melanogenesis. Long-term use of oral TA has also been reported to be effective for melasma when administered for 3 months. Tranexamic acid (trans-4- inomethylcyclohexanecarboxylic acid: TA) is a synthetic lysine analog with antifibrinolytic effect through the reversible blockade of lysine-binding sites on plasminogen molecules. Due to its activity as a plasmin inhibitor, oral TA has been originally utilized in reducing blood loss for management of menorrhagia or major surgery [18,19]. In the dermatological field, it has been used as a topical agent or intradermal injection in melasma patients for its whitening effects [20]. A plasmin inhibitor and lysine analog, trans-4-aminomethylcyclohexanecarboxylic acid (TA), prevents binding of plasminogen to the lysine binding site by interfering with the structure of plasminogen molecules. TA is often used to prevent blood loss during surgery, such as cardiac and oral surgery, joint replacement, and liver transplantation. TA, which has been previously used as hemostatic agent due to its antifibrinolytic effect and is synthetic derivative of amino acid lysine, was first introduced by Nijor in 1979 for treatment of melasma. TA had been used since 1970s under the approval for the treatment of menorrhagia. For this purpose, it is used orally at 2.0–4.5 g/day during the cycles. Up to 4–4.5 g/day of oral medication did not appear to cause any serious adverse effects. It can be cautiously said that oral TA may be a useful adjuvant in melasma patients for several months. However, daily dosage and optimal period of oral TA medication should be further examined. As dose of oral TA in melasma is far less than that prescribed for its hemostatic action, so fatal risks like thromboembolism, myocardial infarction, cerebrovascular accident are very rare. However, it is important to rule out any hypercaogulable state before commencement of treatment.

In an attempt to search for a new treatment for melasma, Wu et al studied oral administration of tranexamic acid (TA) in Chinese patients [21]. Tranexamic acid tablets were prescribed to 74 patients at a dosage of 250 mg twice daily for 6 months. At follow-up, more than half of patients (54%) showed good results. In our study, 80% patients showed good results. This treatment may be effective for some patients, but further study is needed.

In a study by Higashi, Eleven patients with melasma were treated with oral tranexamic acid 0.75-1.5 g/ day [22]. In all cases, hypermelanosis was decreased in a few months after the onset of the medication without adverse reaction. The recurrence of hypermelanosis occurred in a few months after the cessation of the medication. So the effect of the tranexamic acid for melasma is excellent but reversible. The reason why tranexamic acid is effective for melasma is unknown.

A clinical study was conducted with 25 women for eight weeks from March to July 2010 [23].Volunteers were instructed to take two TA tablets three times a day and apply a TA topical agent twice a day for 8 weeks. Twenty-two subjects completed the study and no serious adverse events occurred during the study period. The mean lesional melanin index (MI) scores decreased significantly. Interestingly, the MI scores for the perilesional skin increased. The erythema index scores of lesional and perilesional skin also showed a similar pattern. Histological analysis showed significant reduction of epidermal pigmentation, vessel numbers and mast cell counts. To conclude, TA decreased epidermal pigmentation associated with melasma and also reversed melasma-related dermal changes, such as vessel number and increased numbers of mast cells.

In a study by Amir et al, descriptive cross sectional study of 65 melasma patients was performed (Fitzpatrick skin types III and IV) [24]. Both female and male with moderate to severe melasma were given 250mg oral TA bid for 6 months along with topical sunscreen. 41 patients had good, 15 had excellent and 8 patients had fair improvement. Whereas in our study, 80% shows very good results.None of the patients had serious systemic side effects, only few had oligomenor-

rhoea, palpitation and gastric upset. Patients satisfaction was similarly noted. In our study, gastrointestinal side effects and transient headache were seen in 10% patients.

## Conclusions

To conclude, the response of melisma to oral TA is better and long lasting in comparison to the triple combination. For the treatment of recurrent melasma, oral tranexamic acid provides satisfactory treatment compared to other treatment modalities. But the side effects should be kept in mind before starting the treatment especially since some of the patients are elderly patients with history of cardiac disease and thromboembolism. To conclude, oral administration of TA is a very effective and safe therapy. Further research on the long term administration of TA and reduction of the recurrence rate is needed.

## References


1. Grimes PE. Melasma: etiologic and therapeutic consideration. Arch Dermatol. 1995, 131(12):1453-1457.

2. Azzam OA, Leheta TM, Nagui NA, Shaarawy E, Abdel Hay RM et al. Different therapeutic modalities for treatment of melasma. J Cosmet Dermatol. 2009, 8(4): 275–281.

3. Sheth VM, Pandya AG. Melasma: a comprehensive update: part II. J Am Acad Dermatol. 2011, 65(4):699-713.

4. Kang WH, Chun SC, Lee S. Intermittent therapy for melisma in Asian patients with combined topical agents (retinoic acid, hydroquinone and hydrocortisone): clinical and histolotical studies. J Dermatol. 1998, 25(9):587–596.

5. Maeda K, Naganuma M. Topical Trans 4 Amino Methylcyclohexanecarboxylic Acid Prevents Ultraviolet Radiation Induced Pigmentation. J Photochem Photobiol B. 1998, 47(2-3):130- 141.

6. Maeda K, Y. Tomita. Mechanism of the Inhibitory Effect of Tranexamic Acid on Melanogenesis in Cultured Human Melanocytes in the Presence of Keratinocyte-Conditioned Medium. Journal of Health Science 2007; 53(4): 389-396.

7. Agostoni A, Marasini B, Cicardi M, Martignoni G, Uziel L et al. Hepatic function and fibrinolysis in patients with hereditary angioedema undergoing long term treatment with tranexamic acid. Allergy. 1978, 33(4):216–221.

8. Wellington K, Wagstaff AJ. Tranexamic acid: a review of its use in the management of menorrhagia. Drugs. 2003, 63(3):1417–1433.

9. Lee JH, Park JG, Lim SH, Kim JY, Ahn KY et al. Localized intradermal microinjection of Tranexamic Acid for Treatment of Melasma in Asian Patients: A Preliminary Clinical Trial. Dermatologic Surgery. 2006, 32(5): 626-631.

10. Ennes SBP, Paschoalick RC, Mota de, Avelar Alchorne M. A double-blind, comparative, placebo-controlled study of the efficacy and tolerability of 4% hydroquinone as a depigmenting agent in melasma. J Dermatol Treat. 2000,11(3):173-179.

11. Goldmann MP, Gold MH, Palm MD, Colon LE, Prestone N et al. Sequential treatment with triple combination cream and intense pulsed light is more efficacious than sequential treatment with an inactive (control) cream and intense pulsed light in patients with moderate to severe melasma. Derm Surg. 2011, 37(2):224–233.

12. Kang HY, Ortonne JP. What should be considered in treatment of melasma. Ann Dermatol. –373 :(4)22 ,2010 378.

13. Gupta AK, Gover MD, Nouri K, Taylor S. The treatment of melasma: a review of clinical trials. J Am Acad Dermatol. 1065–1048:(6)55 ,2006.

14. Li D, Shi Y, Li M, Liu J, Feng X. Tranexamic acid can treat ultraviolet radiation-induced pigmentation in guinea pigs. Eur J Dermatol. 292–289 :(3)20 ,2010.

15. Karn D, Kc S, Amatya A, Razouria EA, Timalsina M. Oral tranexamic acid for the treatment of melasma. Kathmandu Univ Med J (KUMJ). 2012, 10(40):40-43

16. Maeda K, Naganuma M. Topical trans4aminometh ylcyclohexanecarboxylic acid prevents ultraviolet radiationinduced pigmentation. J Photochem Photobiol B. 1998, 47(2-3):136–141.

17. Manosroi, Podjanasoonthon K, Manosroi J. Development of Novel Topical Tranexamic Acid Liposome Formulations. Int J Pharm. 2002, 235(1-2): 61-70.

18. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs. 1999, 57(6):1005–1032.

19. Kato H, Araki J, Eto H, Doi K, Hirai R et al. A prospective randomized controlled study of oral tranexamic acid for preventing postinflammatory hyperpigmentation after Q-switched Ruby laser. Derm Surg. 2011, 37(5):605–610.

20. Tsz Wah Tse, Edith Hui. Tranexamic acid: An important adjuvant in the treatment of melasma. Journal of Cosmetic dermatology. 2012, 12(1): 57-66.

21. 21.Wu S, Shi H, Wu H, Yan S, Guo J et al. Treatment of melasma with oral administration of tranexamic acid.

Aesthetic Plast Surg. 2012, 36(4): 964-970.

22. Higashi N. Treatment of melasma with oral tranexamic acid. Skin Res. 1988, 30(5): 676–680.

23. Na JI, Choi SY, Yang SH, Choi HR, Kang HY et al. Effect of tranexamic acid on melasma: a clinical trial with histological evaluation. J Eur Acad Dermatol Venereol. 2012 , 27(8):1035-1039.

24. Safoora Aamir, Riffat Naseem. Oral tranexamic acid in treatment of melasma in Pakistani population: a pilot study. Journal of Pakistan Association of Dermatologists. 2014, 24(3):198-203.